

















# DISEASES OF THE GALL BLADDER AND BILE DUCTS

A BOOK FOR PRACTITIONERS AND STUDENTS

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TO THE MEMORY OF

EDWARD MALLINCKRODT

BENEFACTOR OF SCIENCE, OF EDUCATION AND OF SUFFERING HUMANITY,

WHOSE GENEROSITY HELPED GREATLY IN THE

DEVELOPMENT OF CHOLECYSTOGRAPHY

THIS BOOK IS GRATEFULLY DEDICATED BY THE AUTHORS

to those who wish to acquaint themselves with the more modern ideas of gall-bladder function and diagnosis.

Cholecystography has been discussed extensively; and although the authors may plead a paternal interest as an excuse for what may seem to many an unwarranted confidence in its diagnostic accuracy, an attempt has been made also to present its weaknesses and shortcomings. Much of the criticism against the method has been due to a failure to understand its underlying principles, to inaccuracy of interpretation and to poor technique both in the administration of the substances and in the taking of the roentgen-ray films. It is not a simple automatic procedure, but, as with every other method of diagnosis, experience, intelligence and refined technique are necessary in order to obtain the best results. The early criticisms against the efficiency of the roentgen-ray examination of the stomach and intestinal canal should be recalled in this connection. In addition to the elaborate presentation of the subject of cholecystography, the examination of the gall bladder by ordinary roentgenological means has been amply discussed.

An extensive review of the various tests of liver function in relation to the diagnosis of disease of the gall bladder has been included in the belief that such a review would be welcomed by many who have struggled through some of the extensive literature on this subject. The technique of most of these tests, including that of the van den Bergh test, and of our own test combined with cholecystography, has been given in the hope that the book may prove of value as a reference work to those interested in the performance of those tests.

Throughout the whole book a thread has been followed more or less conspicuously which serves to emphasize the importance of considering disturbances in the liver and other organs as a part of the picture of cholecystitis. Too often the gall bladder has been considered in clinical writings as an isolated structure without due regard for the serious consequences of its disorders upon other viscera.

In the chapter on Treatment the surgical aspects have been extensively presented, but the medical treatment is only briefly discussed because frankly the authors consider non-surgical methods of treatment inefficient except as they are used symptomatically and as a means of preparing patients for operation.

The authors wish to thank the publishers for many courtesies and to acknowledge their gratitude to Mr. Philip A. Conrath, artist of the Department of Surgery of the Washington University School of Medicine, for many of the illustrations.

THE AUTHORS.

ST. LOUIS, MO.



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# DISEASES OF THE GALL BLADDER AND BILE DUCTS.

## CHAPTER I.

### ANATOMY OF THE EXTRA HEPATIC BILE PASSAGES.

THE bile is conveyed from the liver by the *right* and *left hepatic ducts* which issue from the liver at the porta hepatis. These ducts unite to form the *hepatic duct* which passes downward for about 3 cm. to a point where it is joined, usually at an acute angle, by the *cystic duct*. By the union of the cystic duct with the hepatic duct the *common bile duct* (ductus choledochus) is formed. The right and left hepatic ducts, particularly the latter, are formed by the junction of several smaller ducts. The bile from the caudate and Spigelian lobes enters the left hepatic duct. (Fig. 1.) In the dog each lobe has a plainly defined duct. It is possible therefore experimentally to collect the bile separately from each lobe.

The hepatic duct runs downward in the hepato-duodenal ligament (ligamentum hepato-duodenale) to the right of the hepatic artery and in front of the portal vein. The common duct (ductus choledochus) is a continuation of the hepatic duct after its union with the cystic duct from the gall bladder. It is about 7 cm. long and normally its lumen is about 3 mm. in diameter (a little smaller than an ordinary lead pencil). It runs in the right border of the lesser omentum, and therefore anterior to the foramen of Winslow, passes behind the superior portion of the duodenum and then runs in a groove on the posterior surface of the head of the pancreas. (Plate I.) At this place it lies in front of the inferior vena cava. At times it is completely imbedded in the substance of the pancreas. For a short distance it lies along the right side of the terminal part of the pancreatic duct and with it passes obliquely through the wall of the duodenum. The distance traversed in the wall of the duodenum by the common bile duct varies from 1 to 3 cm. After uniting, the two ducts open by a common orifice at a papilla (*papilla*

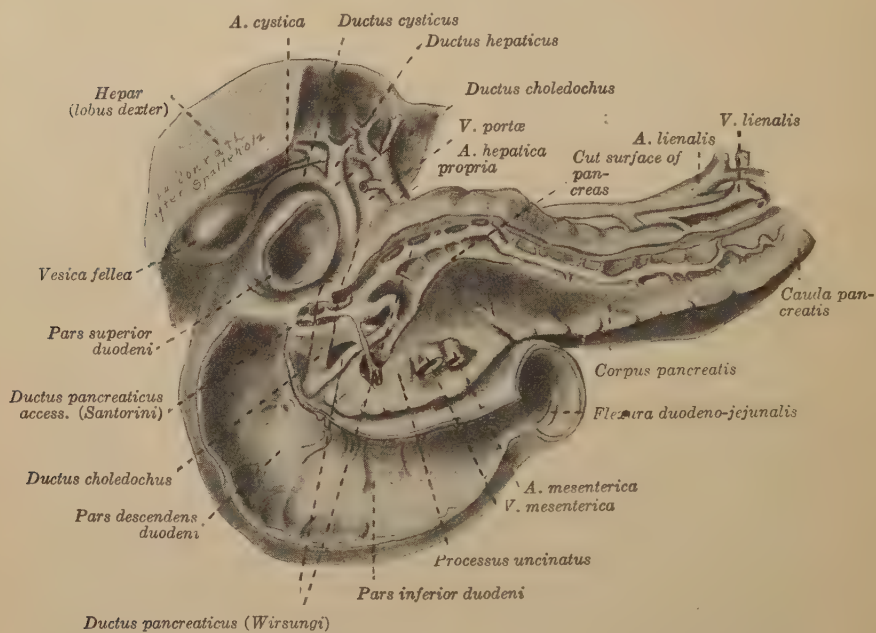


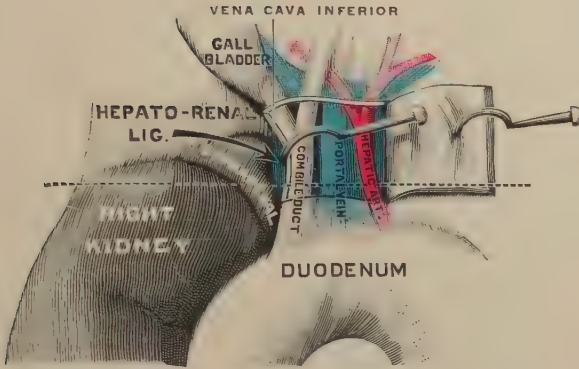
FIG. 1.—Excretory ducts of the liver and pancreas. (After Spalteholz.)



FIG. 2.—The four types of anastomosis between ductus choledochus and duct of Wirsung, seen in cross-section of the duodenal wall. (From Letulla and Nattan-Larrier.)

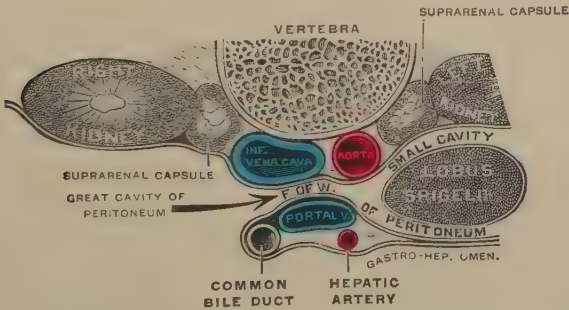


## PLATE I



### Dissection to Show Relations of the Foramen of Winslow, to Which the Dart Points.

The front of the right portion of the gastro-hepatic omentum has been cut and turned off to the left, and the liver lifted up and back, displaying the objects in the front wall of the foramen. The horizontal broken line marks the position of the section from which the next picture was made. (Testut.)



### Transverse Horizontal Section Through the Foramen of Winslow.

The lower end of the Spigelian lobe has been shaved off, and the upper surface of the piece is seen. (Testut.)



*duodeni*), about 7 to 10 cm. from the pylorus, located at the mesial side of the descending portion of the duodenum. The union of the two ducts, dilated into an ampulla, is known as the *Ampulla of Vater*. (Figs. 2 and 3.) Job,<sup>1</sup> however, in a recent study of human cadavers has found a typical ampulla to be infrequent. He states that the usual arrangement is for the two ducts to be separated at the tip of the duodenal papilla.

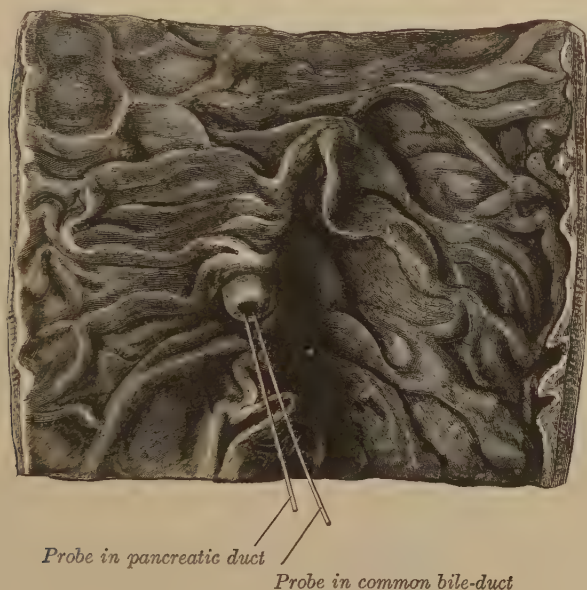


FIG. 3.—Interior of the descending portion of the duodenum, showing bile papilla. (Gray.)

The gall bladder is usually described as a pear-shaped sac lying in a fossa on the under surface of the right lobe of the liver and extending to its anterior margin from the *porta hepatis*. Its normal color is slate blue and it is slightly translucent. A thin tracery of small bloodvessels is seen on its surface. Ordinarily the gall bladder is covered by the peritoneum of the under surface of the liver except on its upper aspect where it is united to the fossa of the liver by thin, loose, areolar tissue. Occasionally it is completely covered by peritoneum with a mesenteric attachment to the liver. Sometimes also it is completely imbedded in the liver substance, but this is a very rare occurrence. The lower, wider part is usually

<sup>1</sup> Job, T. T.: The Anatomy of the Duodenal Portion of the Bile and Pancreatic Ducts, *Anat. Rec.*, 1926, 32, 212.

called the *fundus* and the upper part which joins the cystic duct is called the neck (*collum*). The intermediate portion is often called the body (*corpus*). The upper part of the corpus has been given by some the separate name of *infundibulum*. This latter part is sometimes enlarged in pathological conditions to give the appearance almost of a diverticulum, and it may be prolonged for some distance to lie parallel to the cystic duct. Normally the gall bladder is from

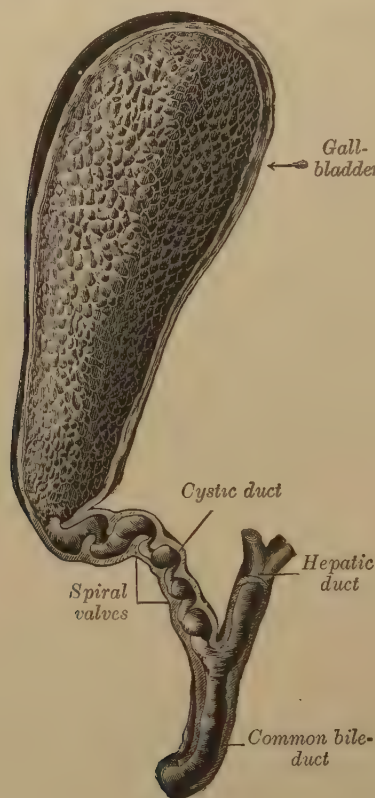


FIG. 4.—The gall bladder and bile-ducts laid open. (Spalteholz.)

about 7 to 10 cm. in length, about 3 cm. in breadth at its widest part, and its capacity varies from about 30 to 50 cc. (Fig. 4.) The gall bladder and bile-ducts lie in Morrison's pouch, or the subhepatic space, bounded above by the under surface of the right lobe of the liver, below by the transverse colon and mesocolon, externally by the parietes down to the iliac crest, and internally by the peritoneum covering the spine. It is said that this space can hold nearly a pint

of fluid with the patient in the supine position. It can be drained adequately by a lumbar incision.

The fundus of the gall bladder is directed downward, forward and to the right, and it projects slightly beyond the anterior margin of the right lobe of the liver. Because of this fact it comes into relationship with the anterior abdominal wall. Posteriorly the fundus is in relationship with the transverse colon. The body comes into relationship, by its upper surface, with the liver; by its under surface with the commencement of the transverse colon and more posteriorly with the descending portion of the duodenum and sometimes with the superior portion of the duodenum or the pyloric portion of the stomach. The neck pursues an S-shaped curve inward toward the portal fissure, and when distended it presents the appearance of a spiral construction which is continuous with the cystic duct and is due to crescentic folds arranged somewhat spirally around the interior of its cavity.



FIG. 5.—The valves of Heister as portrayed in his original work, *Compendium Anatomicum*, Amsterdam, 1723. (After Sweet.)

The cystic duct ordinarily is about 3 or 4 cm. long. It passes backward, downward and to the left from the neck of the gall bladder to join the common hepatic duct. The mucous membrane of the cystic duct is thrown into a number of from five to twelve crescentic folds, the so-called *valves of Heister*. (Figs. 5 and 6.)

Microscopically the gall bladder is found to consist of a mucosa, a fibromuscular coat, a subserous coat and the serosa. The mucous membrane is thrown into tufts or folds which correspond with ridges in the underlying fibro-muscular coat. These are covered by a single layer of columnar epithelial cells. Boyd,<sup>1</sup> in his interesting article dealing particularly with the lipoid deposits in the gall bladder, states: "In text-books of anatomy one reads the statement that the mucous membrane of the normal gall bladder is thrown into folds. But this conveys little to the mind until the gall bladder wall is viewed direct under the dissecting binocular microscope. When the fresh gall bladder, immersed in water, is observed by

<sup>1</sup> Boyd, William: *Studies in Gall Bladder Pathology*, *British Jour. Surg.*, 1922, 10, 337.



reflected daylight or, still better, by the brilliant light of an electric arc, the picture is a remarkable and beautiful one. As if one were gazing into the depths of a marine pool at sea-weeds and sea-anemones, tall graceful folds and membranes, gossamer-like in their delicacy, can be seen floating in the ambient fluid. The entire inner surface is divided by these membranes into a series of polygonal spaces, and each of these spaces resembles a little courtyard surrounded by high though delicate walls. In microscopic sections the membranes, cut transversely, appear as villi. They are not true villi, but the term is allowable because of its convenience. It

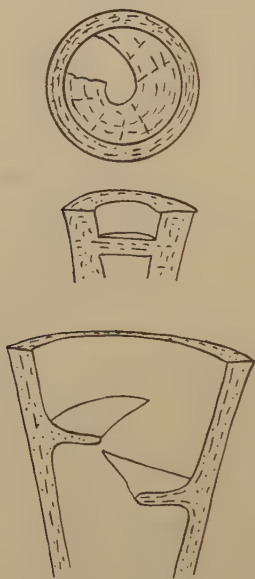


FIG. 6.—Cystic duct of man showing Heisterian valve. (After Hendrickson.)

is a striking picture and, as we shall see later, one which at once suggests that the idea of the gall bladder's being a mere reservoir is absolutely untenable. Such a highly specialized structure can be for one purpose only, and that purpose is absorption." The columnar epithelial cells secrete mucus, and at times they are seen to contain so much mucus that they resemble goblet cells. Whether or not true mucous glands are present is a much-debated question, but certainly they are not so frequent as is commonly stated. Some of the supposed mucous glands are probably nothing more than cross sections of the projecting tufts. Lütken states definitely that

mucous glands occur both in the infundibulum and collum of the gall bladder, as well as in the cystic, hepatic and common ducts. He states that the secretions from these glands give the reactions for mucin. Halpert<sup>1</sup> states that glands of alveolar and tubulo-alveolar form are occasionally seen in the neck of the gall bladder but nowhere else. The so-called Rokitansky-Aschoff sinuses, deeper outpouchings of the mucosa toward the external layers, have often been confused with these glands, although the two have no relation whatever to one another. The literature on the matter of these glands is given by Shikunami.<sup>2</sup> In recent years the occurrence of deposits of lipid material in the mucous membrane of the gall bladder has attracted much attention. For that reason, the finding by Boyd that the dried mucosa of the normal gall bladder contains from 0.51 to 1.70 per cent of cholesterol is of interest. This amount is to be compared with as much as 60.54 per cent of cholesterol which he found in one case of "strawberry" gall bladder. The lipid deposits occur almost entirely in the epithelial cells of the mucosa; almost none are seen in the other coats. According to Halpert,<sup>3</sup> Virchow<sup>4</sup> first observed them in 1846, and in 1857 he considered these cells as being concerned with the intermediate metabolism of fats, considering a part of the fats of the bile to be reabsorbed by the gall bladder mucosa.

The fibro-muscular coat is composed of elastic tissue in which bands of smooth muscle are laid down. Hendrickson<sup>5</sup> states that there are no definite layers of muscle in the gall bladder, but others have described three indefinite layers, longitudinal, oblique and circular, of which the thickest runs transversely, or in a circular manner. The portion of the fibro-muscular coat which is just beneath the mucosa is composed chiefly of connective tissue, and it corresponds somewhat with the submucosa of other organs. Halpert<sup>6</sup> calls attention to the fact that the muscle of the whole organ, in respect to both location and amount bears a striking resemblance to the muscularis mucosæ of the intestine, and he suggests that perhaps its chief function is to throw the mucous

<sup>1</sup> Halpert, B.: *Morphological Studies on the Gall Bladder*. 1. A Note on the Development and the Microscopic Structure of the Normal Human Gall Bladder, *Bull. Johns Hopkins Hosp.*, 1927, **40**, 390.

<sup>2</sup> Shikunami, J.: *Beitrage zur mikroskopischen Anatomie der Gallenblase*, *Anat. Hefte*, 1908, **36**, 551.

<sup>3</sup> Halpert, B.: *Ibid.*

<sup>4</sup> Virchow, R.: *Ueber das Epithel der Gallenblase und über einen intermediären Stoffwechsel des Fettes*, *Virchow's Arch.*, 1857, **11**, 574.

<sup>5</sup> Hendrickson, W. F.: *A Study of the Musculature of the Entire Extrahepatic Biliary System*, *Johns Hopkins Hosp. Bull.*, 1898, **9**, 221.

<sup>6</sup> Halpert, B.: *Ibid.*

membrane into folds. He also notes the interesting fact that there is a gradual decrease of the musculature toward the fundus and a slight increase toward the collum. With such an arrangement it would be difficult to understand how the gall bladder could empty itself by intrinsic muscular contractions, a subject fully discussed in the chapter on Physiology of the Gall Bladder. Furthermore he found that in the two-toed sloth the musculature of the liver side of the gall bladder was missing in some places and scant in others as compared with the relatively large amount of musculature on the peritoneal surface. But even so, the latter comprised only about one-third of the entire circumference of the viscus. Halpert has also studied the formation of the Rokitsansky-Aschoff sinuses with relation to the musculature. He finds that these are probably merely outpouchings of mucosa into defects in the muscularis, and that the most favorable sites for the formation of such sinuses are where the vessels penetrate the muscularis to reach or leave the mucosa. He concludes also that these sinuses are very rarely seen in the healthy human gall bladder and that they are almost always a manifestation of disease. Boyden<sup>1</sup> has recently made an extensive investigation of the whole matter of the relative amounts of elastic tissue and muscle in the wall of the gall bladder, as has also Lütken.<sup>2</sup> Both find that there is much less muscle than elastic tissue. The subserous coat is composed almost entirely of interlacing elastic tissue fibrils. The serosa is the reflection of the peritoneum on the gall bladder from the liver. (Figs. 7, 8 and 9.)

The hepatic, cystic and common bile ducts all possess a mucosa, a submucosa and a muscularis. The mucosa consists of a single layer of columnar epithelium and a tunica propria which contains mucous glands and a few muscle fibers. The submucosa is a thick layer of connective tissue. The muscularis of all the ducts, according to Hendrickson, consists of a distinct transverse longitudinal and diagonal layer of smooth muscle arranged in a somewhat plexiform manner. The Heisterian valves of the cystic duct also contain muscle. The transverse fibers of the cystic duct run in a circular direction in the valve, as if the wall at this level had been invaginated. Most of the longitudinal fibers continue down the duct, but a few enter the valve almost at right angles. The diagonal fibers apparently do not enter the valve. In the hepatic duct the

<sup>1</sup> Boyden, E. A.: The Effect of Natural Foods on the Distention of the Gall Bladder; with a Note on the Change in Pattern of the Mucosa as it Passes from Distention to Collapse, *Anat. Rec.*, 1925, **30**, 333.

<sup>2</sup> Lütken, U.: *Aufbau und Funktion der Extrahepatischen Gallenwege*, 1926, F. C. W. Vogel, Leipsig.

longitudinal fibers are most numerous. There are only a few transverse and diagonal fibers. There is much connective tissue between the muscle fibers. In the common bile duct all three types

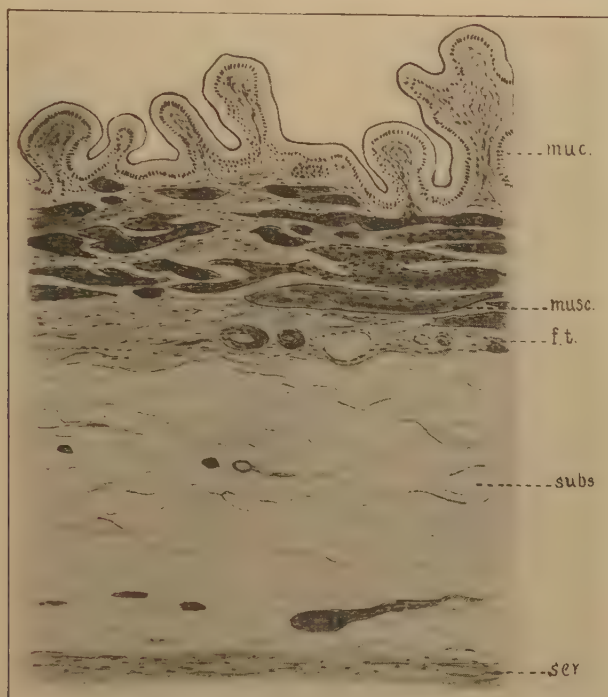


FIG. 7.—Normal human gall bladder. *muc.*, mucosa; *musc.*, muscularis; *f.t.*, fibrous tunic; *subs.*, subserosa; *ser.*, serosa.

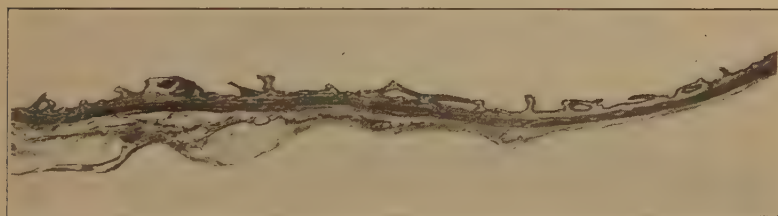


FIG. 8.—A cross-section of a normally distended cat's gall bladder of a fasting animal ( $\times 29$ ). The entire wall, on the right, measures 0.16 mm. in thickness, the mucosa constituting half of the thickness (0.08 mm.), the rest being equally divided between the muscularis and the serosa (0.04 mm. each). (After Boyden.)

of fibers were found, but the diagonal ones were least numerous. Again, here, much connective tissue was found between the muscle fibers.



As regards the duodenal portion of the human common bile duct, Hendrickson<sup>1</sup> states that many individual variations in structure



FIG. 9.—A cross-section of a fully collapsed cat's gall bladder, six and one-half hours after eating a meal of yolk and cream ( $\times 29$ ). In this specimen the entire thickness of one wall measures 2.3 mm., nearly fifteen times that in Fig. 8, the mucosa constituting 1.5 mm., the other two layers 0.4 mm. each. Comparing the two figures, it is seen that in passing from distention to collapse, the muscularis and serosa each increase in thickness ten times, while the mucosa is increasing its thickness nearly nineteen times. (After Boyden.)

occur but that these variations do not alter the general anatomical bearing of this region. As a common type he presents the three accompanying drawings.

"Fig. 10 shows the entrance of the common bile-duct *B* and the duct of Wirsung *W* into the intestinal wall. We see a simple separation of the fibers of the outer longitudinal muscular coat of the intestine *L I*. The common bile-duct and the duct of Wirsung pass through this separation. At *F* we find muscle fibers arising from the outer longitudinal muscular coat. These fibers run up on the common bile-duct and becoming gradually less and less marked, finally disappear. This arrangement is bilateral. The fibers marked *I R* represent some bundles of muscle which (shown in Fig. 12, *I R*) form an independent ring of muscle around the common bile-duct between it and the duct of Wirsung. At *H* are seen muscle fibers which run almost entirely around the duct of Wirsung, but

<sup>1</sup> Hendrickson, W. F.: A Study of the Musculature of the Entire Extra-hepatic Biliary System, Johns Hopkins Hosp. Bull., 1898, 9, 221.



as these fibers approach that side of the pancreatic duct nearest the common bile-duct, they turn abruptly and run up on the duct of Wirsung in a longitudinal direction. They gradually diminish in volume as they ascend the duct. This structure is bilateral. See also Fig. 12, *H*.

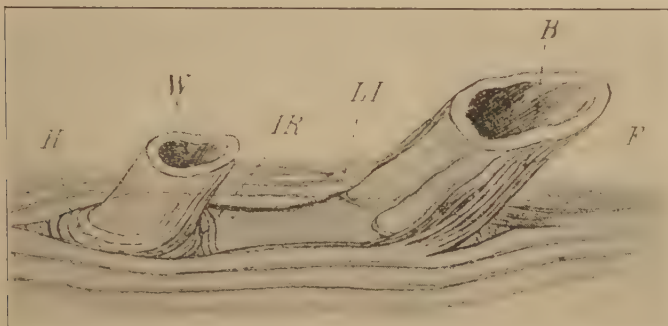


FIG. 10.—The entrance of the common bile-duct *B* and the duct of Wirsung *W* into the intestinal wall. (After Hendrickson.) (See page 26.)

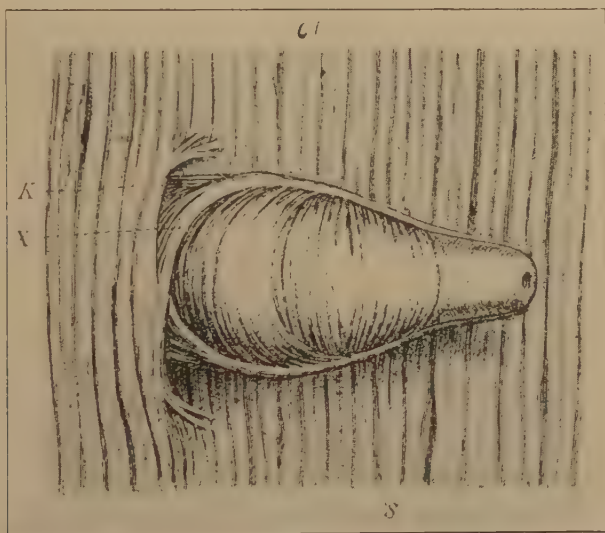


FIG. 11.—Structures seen after removal of the mucous membrane from the intestinal wall in the region of the duodenal papilla. (After Hendrickson.)

“Fig. 11 represents the structures seen upon removal of the mucous membrane from the intestinal wall in the region of the duodenal papilla. The inner circular muscular coat of the intestine is represented by *CI*. The first point to demand attention is the penetration of the inner circular muscular coat by the common bile-duct. At the spot of penetration there is a simple separation of the muscle bundles of the inner circular muscle

coat. It should be noted that the human specimen differs from the arrangement found in the dog. In the latter animal the inner circular muscle coat forms a tube-like structure which embraces the common bile-duct for a considerable distance. In man the common bile-duct plunges immediately through the muscle layer which composes the inner circular muscular coat. At *S* bundles of muscle running around the common bile-duct (see also Fig. 12, *S*). These are independent rings of muscle which embrace the duct. Now, if we look further back on the common bile-duct, near the point at which it penetrates the inner circular muscular coat, we observe muscle bundles *X* which do not run entirely around the duct. These muscle bundles are very intimately mixed with the independent muscle rings which completely embrace the duct. The former, however, upon reaching the level of the inner circular muscle coat, turn abruptly forward and under the bile-duct, and after running for some distance toward the duodenal papilla finally end in the connective tissue of the submucosa of the intestine (see also Fig. 12, *X*). This arrangement is bilateral. The

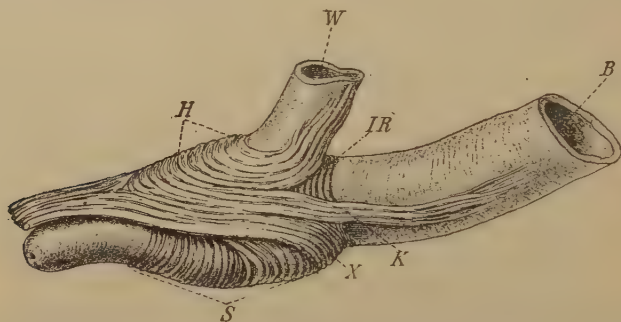


FIG. 12.—Muscular arrangement about the end of the common bile-duct and the duct of Wirsung after all fibers of the outer longitudinal and inner circular muscle coats have been removed. (After Hendrickson.)

drawing shows that this arrangement of muscle about the common bile-duct begins at a point before the duct penetrates the inner circular muscular coat. In this particular specimen, a muscle bundle of the inner circular muscular coat curves around and becomes continuous with the fibers marked *X*. It may be well to note that the *X* fibers did not terminate in all cases according to this description. In several cases these fibers, after turning forward and under the common bile-duct, decussated with similar ones from the opposite side and after such decussation became continuous with the fibers of the inner circular muscular coat of the intestine. In one case the *X* fibers after turning forward suddenly plunged through the inner circular muscle coat and became continuous with the fibers of the outer longitudinal muscle coat of the intestine. In some specimens, after dissecting away the *S* fibers, a few longitudinally and diagonally disposed fibers were seen. These had origin in those fibers of the outer longitudinal and inner circular muscle coat which lie over the common bile-duct when viewed as in Fig. 11. Finally in Fig. 11 a bundle of muscle fibers *K* can be seen on each side of the common bile-duct running parallel with it.

These bundles arise on the surface of the common bile-duct (Fig. 12, *K*) and are covered by the *F* fibers of Fig. 10. In this case they run forward from under the inner circular muscular coat (see Fig. 11, *K*) and bend around beneath the common bile-duct, becoming continuous with each other, thus forming a loop around the duct of Wirsung, Fig. 12, *K*. In other specimens these *K* fibers originate in the same way but terminate by running under the common bile-duct and decussating there with similar fibers from the opposite side.

"Fig. 12 shows the muscular arrangement about the end of the common bile-duct and the duct of Wirsung after all fibers of the outer longitudinal and inner circular muscle coats have been removed. The common bile-duct and the duct of Wirsung have been drawn in the same position as they occupied in Fig. 10, but removal of the muscular coats of the intestine permits of a view of the various structures in profile. All the structures here shown have been described more or less fully under Figs. 10 and 11."

The sphincteric arrangement of muscle fibers around the common bile-duct in its duodenal portion is usually called by the name of Oddi,<sup>1</sup> an Italian who described it in 1886. However, as Hendrickson states, the presence of a sphincter muscle at this location was suspected by Glisson<sup>2</sup> as early as 1681. Also Boyden<sup>3</sup> has found that as early as 1879 Gage,<sup>4</sup> an American anatomist, described the sphincter as follows: "As the ductus choledochus and duct of Wirsung pass through the longitudinal muscular coat of the duodenum they are provided by it with a common, and each with a special sphincter."

In a recent study of this region based on the dissection of 151 cadavers, Job<sup>5</sup> has concluded that the musculature of the duodenal wall does not form an efficient sphincter of these ducts. Each duct has an individual circular and longitudinal smooth-muscle layer and a common circular and longitudinal layer almost to the tip of the papilla. Just inside the gut wall the bile-duct has a very definite sphincter, and from this point on the two layers of muscle decrease until the longitudinal layer disappears 1 or 2 mm. from the tip of the papilla, the circular layer persisting to the tip, though only a few cells. The common and individual muscle layers seem to intermingle at various points.

<sup>1</sup> Oddi, R.: Di una speciale disposizione a sfintere allo sbocco del coledoco, *Ann. d. Univ. libera di Perugia, Fac. di med. e chir.*, 1886-1887, **2**, 249.

<sup>2</sup> Glisson, Francis: *Anatomia hepatis; cui praemittuntur quaedam ad rem anatomicam universe spectantia. Et ad calcem oferis subjiciuntur nonnulla de lymphae ductibus nuper repertis*, Hagae, A. Leers, 1681.

<sup>3</sup> Boyden, E. A.: The Effect of Natural Foods on the Distention of the Gall Bladder; with a Note on the Change in Pattern of the Mucosa as it Passes from Distention to Collapse, *Anat., Res.* 1925, **30**, 333.

<sup>4</sup> Gage, S. H.: The Ampulla of Vater and the Pancreatic Ducts in the Domestic Cat, *Am. Quart. Micr. Jour.*, 1879, vol. **1**.

<sup>5</sup> Job, T. T.: The Anatomy of the Duodenal Portion of the Bile and Pancreatic Ducts, *Anat. Rec.*, 1926, **32**, 212.

### BLOOD SUPPLY OF THE GALL BLADDER.

The blood supply to the gall bladder comes through the cystic artery which is a branch usually of the right hepatic artery. The relationship of the arteries to the ducts is subject to great variation as will be discussed later. However, the most common arrangement, as found by Flint,<sup>1</sup> is for the cystic artery to arise from the right hepatic artery just to the right of the common hepatic duct. Apparently this agrees also with the conclusions of Eisendrath.<sup>2</sup> The arteries penetrate the wall of the gall bladder and divide in the fibro-muscular coat near the subserous layer. Arterial branches are given off to the mucosa, in which a fine network is found, and to the subserous and serous coats. The veins run in the fibro-muscular coat. These veins empty into the cystic vein which drains into the portal vein and not, as might be expected, into an hepatic vein. The veins also from the ducts drain into the portal vein by way of the cystic vein.

### LYMPHATICS OF THE GALL BLADDER.

The lymphatics of the gall bladder have been extensively studied by Sudler<sup>3</sup> from whose work the following account is largely taken. The large lymphatic vessels running over the gall bladder bring lymph from the liver and the coats of the gall bladder. They follow the inner side of the cystic duct and end in mesenteric lymph glands. Poirier and Charpy<sup>4</sup> state that these vessels unite with those from the quadrate lobe and pass into a gland which is nearly constant and called by them the "gland of the neck," or into the glands of the hilum, or porta hepatis. This "gland of the neck" is often enlarged in cases of cholecystitis, and it therefore becomes of considerable surgical importance, as will be seen later in the section on diagnosis. Lund gave it the special name of "sentinel gland." Occasionally two glands, instead of one, are present at this site, which may be near the neck of the gall bladder or on the cystic duct near its junction with the common duct.

In the subserous layer there is a network of lymph channels which

<sup>1</sup> Flint, E. R.: Abnormalities of the Right Hepatic, Cystic and Gastro-duodenal Arteries, and of the Bile Ducts, *British Jour. Surg.*, 1922, **10**, 509.

<sup>2</sup> Eisendrath, D. N.: Anomalies of the Bile Ducts and Bloodvessels, *Jour. Am. Med. Assn.*, 1918, **71**, 864.

<sup>3</sup> Sudler, M. T.: The Architecture of the Gall Bladder, *Bull. Johns Hopkins Hosp.*, 1901, **12**, 126.

<sup>4</sup> Poirier, P. and Charpy, A.: *Traite d'Anatomie Humaine*, Paris, Masson et Cie, 1901, **4**, 814.



empty into these larger vessels. This network is very irregular and the lymph channels vary markedly in size and shape. The sub-mucous sets of lymphatics are in the connective tissue just under the mucous membrane. However, they rarely run up into the connective-tissue folds but are at their lowest part or more frequently just at their base. The network is almost entirely absent in the dense muscular part. There are normally no solitary lymph follicles in the gall bladder similar to those found abundantly in the appendix.



FIG. 13.—Lymphatics of gall bladder of pig. (After Sudler.)

One of the most important points about the lymphatics of the gall bladder is the fact that, as is seen in the accompanying illustrations, they have a very intimate anastomosis with those of the liver.<sup>1</sup> (Figs. 13, 14 and 15.)

<sup>1</sup> Since the preparation of this manuscript we have seen the article by Winkewer (A Study of the Lymphatics of the Gall Bladder of the Cat, Bull. Johns Hopkins Hosp., 1927, 41, 226) which states that in the cat he was unable to obtain evidence that lymph from the liver reaches the gall bladder or *vice versa*. This finding is at such variance with the results of others who have studied the human, the dog's and the pig's gall bladder that further work should be done to see if the cat is an exceptional animal in this respect.

The lymphatics of the ducts are said by Poirier and Charpy to be arranged as follows: Those of the hepatic, cystic and upper part

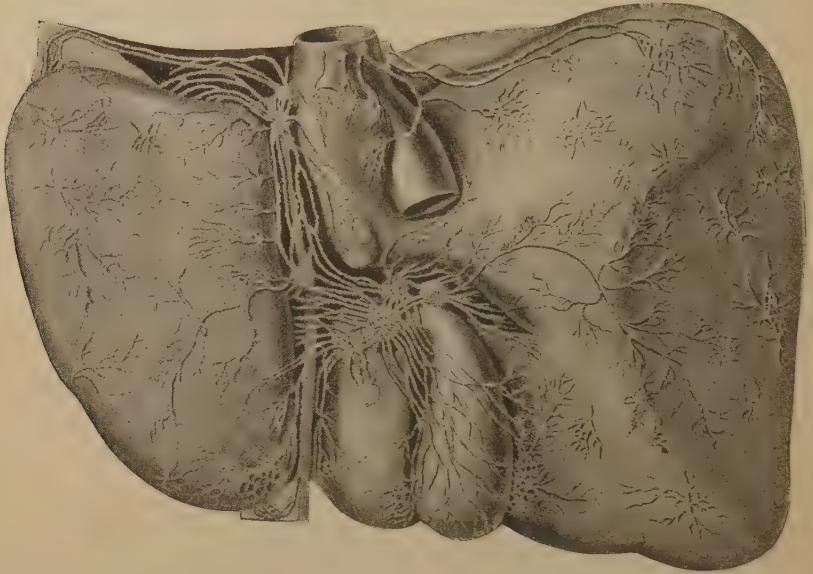


FIG. 14.—Lymphatics of the liver and gall bladder, posterior view. (Modified from Sappey.)

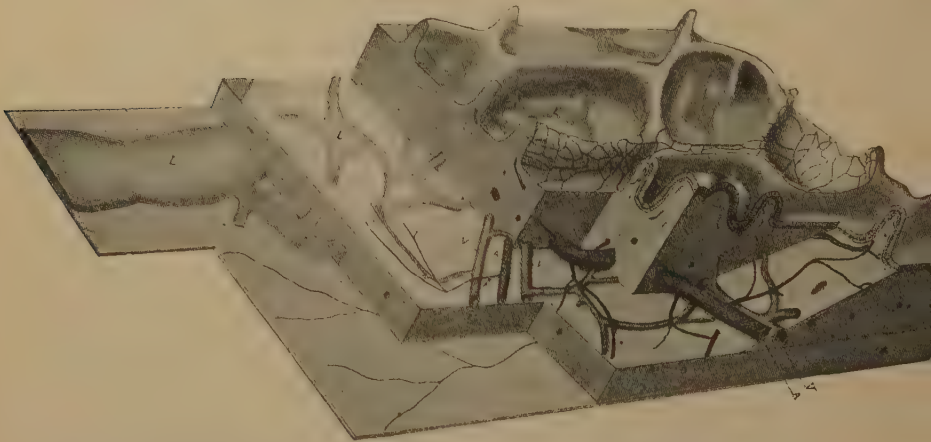
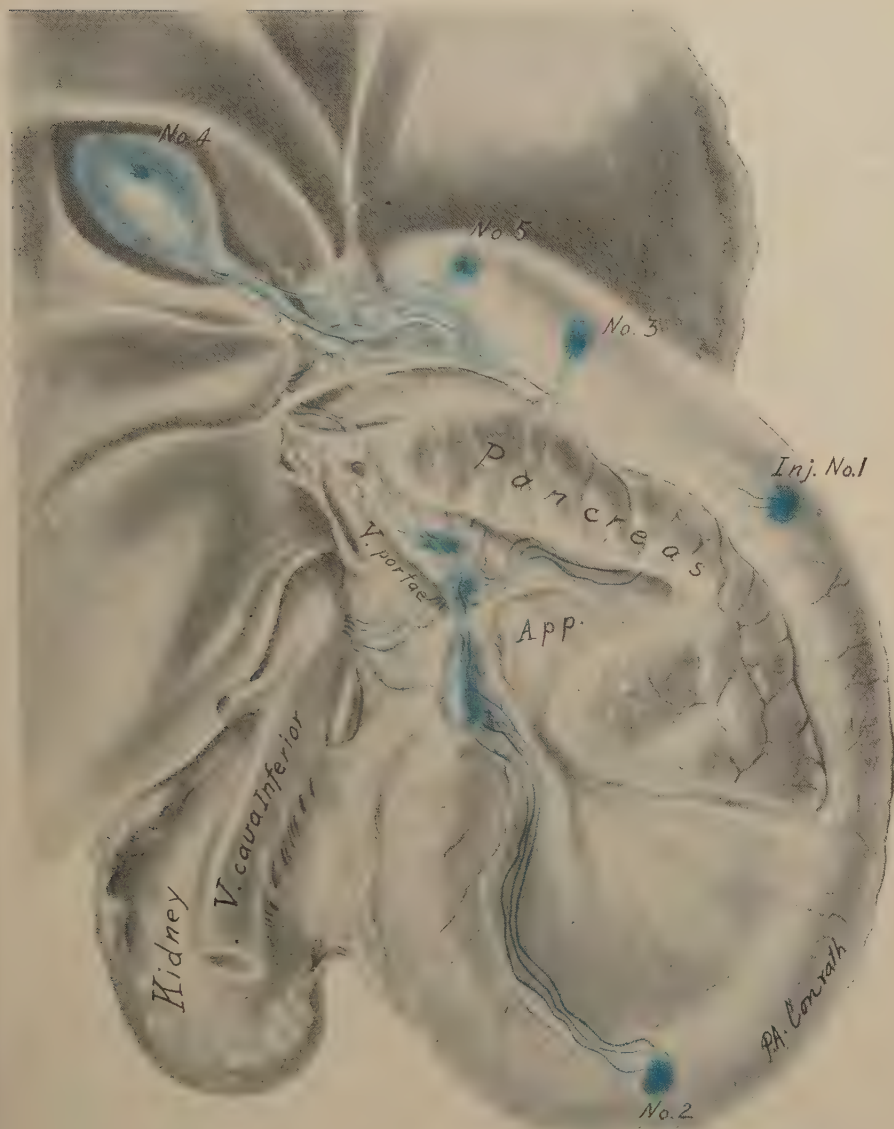


FIG. 15.—Reconstruction of wall of a dog's gall bladder. A, artery; v, vein; L, lymphatic ( $\times 60$ ). (Sudler.)

of the common duct drain into the glands at the hilum. Those at the lower end of the common duct probably drain into the glands in the neighborhood of the head of the pancreas.

# PLATE II



## Distribution of Lymphatics about the Gall Bladder, Duodenum and Portal Vein in the Dog.

The duodenum and pancreas have been rotated to the left so that the posterior surface of each is exposed to view. Trypan blue injected into subserosal lymphatics of gall bladder at site 4 passes through lymphatic vessels to the first portion of the duodenum (the ulcer portion) at site 5 and to the glands about the portal vein. Conversely also, when an injection is made at site 5 most of the fluid passes through lymphatic vessels to the gall bladder. The importance of this from the standpoint of the association of cholecystitis and duodenal ulcer is obvious. When subserosal injections are made in the duodenum at sites 3 and 1, the fluid passes over the pancreas to the lymph nodes about the portal vein. After a subserosal injection of the appendix, which is situated high in the dog, and the pancreas, the dye may be traced in the lymphatics to the nodes about the portal vein.

*The Lymphatics of the Extrahepatic Biliary Passages.*—Shuichi Kodama.  
*Surgery, Gynec. and Obst.*, 1926, vol. 43, p. 140.



Kodama,<sup>1</sup> in our laboratory, has recently carried out a series of experiments concerning the relationship and possible connections between the lymphatics of the extra-hepatic biliary passages and those of other abdominal organs. The investigation is important because of associated pathological disturbances in the biliary system and in other organs. These disturbances are discussed in the section on pathology. Kodama used as an injection solution 1 gm. trypan blue, 5 gm. gelatin, water up to 100 cc. When this was injected slowly into the subserosa of the upper part of the first portion of the duodenum of the dog it was found to pass through the lymphatic vessels along the common duct and to enter the wall of the gall bladder. (See injection point 5 in Plate II.) Likewise, when the solution was injected into the lymphatic vessels immediately beneath the serosa of the gall bladder or at the entrance of the portal vein into the liver, the dye was carried to the upper part of the duodenum and to the lymph glands alongside the portal vein. The dye was also seen in the lymphatic vessels on the surface of the right tail of the pancreas and in the lymph gland at the beginning of the portal vein. (See injection point 4 in Plate II.) This finding that the lymph drainage from the gall bladder passes over the surface of the pancreas and does not enter its substance, agrees with Archibald's<sup>2</sup> contention and is in disagreement with the findings of Maugeret,<sup>3</sup> Deaver and Sweet,<sup>4</sup> and Graham and Peterman,<sup>5</sup> all of whom concluded from their experiments that the lymphatic vessels from the gall bladder pass through the pancreas. Kodama's findings concern the normal dog. If, however, the gall bladder was adherent to the surface of the pancreas, then a direct anastomosis between the lymphatics of the gall bladder and those of the parenchyma of the pancreas was found to exist. When Kodama injected the middle or third portion of the duodenum he found that the dye did not pass into the lymphatics of the gall bladder but that instead it entered the mesenteric lymph gland which is situated at the beginning of the portal vein after passing through the lymphatic vessels

<sup>1</sup> Kodama, S.: The Lymphatics of the Extra-hepatic Biliary Passages, Surg., Gynec. and Obst., 1926, **43**, 140.

<sup>2</sup> Archibald, E.: The Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common Duct Sphincter, Surg., Gynec. and Obst., 1919, **28**, 529.

<sup>3</sup> Maugeret, R.: Cholécycte—Pancréatite, Thèse, Paris, G. Steinheil, 1908.

<sup>4</sup> Deaver, J. B. and Sweet, J. E.: Prepancreatic and Peripancreatic Disease; with a Consideration of the Anatomic Basis of Infections from the Gall Bladder to the Pancreas, Jour. Am. Med. Assn., 1921, **77**, 194.

<sup>5</sup> Graham, E. A. and Peterman, M. G.: Further Observations on the Lymphatic Origin of Cholecystitis, Cholelithiasis, and the Associated Pancreatitis, Arch. Surg., 1922, **4**, 23.



under the peritoneum between the duodenum and the portal vein. These lymphatic vessels were found to pass over the pancreas rather than to enter it, contrary to the finding of Bartels.<sup>1</sup> (See injection points 3, 2 and 1 in Plate II.) Kodama could find no direct lymphatic connection between the gall bladder and any other part of the intestinal tract than the upper part of the duodenum. He made the additional observation, however, that in the dog there are usually three lymph glands along the portal vein, of which two are placed on the anterior surface of the vein and one of them posterior to it. The lymph from the right lobe of the liver enters chiefly the gland posterior to the portal vein, but that from the other lobes and from the gall bladder enters the glands anterior to the vein.

### NERVES OF THE GALL BLADDER.

The nerves of the gall bladder and extra-hepatic ducts are derived from the same source as those which go to the liver. They arise chiefly in the plexus hepaticus which surrounds the portal vein and the hepatic artery. Some fibers course along the choledochus and can be seen on the surface. The nerves go chiefly to the muscular elements of the biliary passages and are dependent upon the sympathetic system. The study of the disposition of the fibers has been made especially in the gall bladder. In the bed of circular fibers is found a plexus designated the *principal plexus*. In spite of its very irregular arrangement, one might compare it anatomically with Auerbach's plexus in the intestine. The principal plexus contains cellular elements belonging to several types, according to Dogiel.<sup>2</sup> The cells, grouped in places in small ganglia, represent motor, sensory and association neurones which one can differentiate by their form and by their relations. The motor cells recall the multipolar elements of the sympathetic ganglia. The principal plexus furnishes: (1) Motor fibers to the media and the wall of the vessels, and (2) other fibers which form in the mucosa a secondary plexus. Ranvier was able to follow certain fibers of this secondary plexus right up to the epithelium, but he has not observed any intra-epithelial terminations. These fibers may very reasonably be considered as sensory. Doyon considered that from experimental evidence of his own the ganglia of the plexuses of the gall bladder

<sup>1</sup> Bartels, P.: Ueber die Lymph gefaesse des Pankreas, Arch. f. Anat. u. Entwicklungsgesch., 1906, p. 250.

<sup>2</sup> Dogiel, A. S.: Ueber den Bau der Ganglien in den Geflechten des Darmes und der Gallenblase des Menschen und der Säugethiere, Arch. f. Anat. u. Entwickl., 1899, p. 130.

function as an automatic peripheral center; but later work has cast doubt on the validity of Doyon's conclusions. See the section on the physiology of the gall bladder for a more extensive discussion of this point.

With reference to Dogiel's findings quoted above, Huber<sup>1</sup> states: "In the gall bladder and bile-duct, as Dogiel has observed, there are to be found medullated nerves which do not end in the sympathetic ganglia. In the gall bladder, owing perhaps to the presence of the bile, or to the brownish stain of the epithelium, I have not been able to make out the endings of such fibers. In one methylene blue preparation of the bile duct of a cat, I was able to make out several arborizations in the mucosa—thus above the muscular coat—and from one of these some few terminal branches could be traced into the epithelium."

Lütken's<sup>2</sup> has also made a study of the distribution of the nerves in the extrahepatic bile passages. He finds that ganglion cells are sparse in the muscular layer of the gall bladder and in the distal end of the common duct near the sphincter of Oddi. They are also few in number in the mucosa and they occur in small numbers at the border of the tunica propria and the subepithelial connective tissue layer of the gall bladder. In only one specimen did he find them in the wall of the upper part of the common duct. Most of the ganglion cells are to be found in the cystic duct, especially in the fibro-muscular layer, as has been described by Aschoff and Bacmeister. In this duct they are most numerous in the middle portion, and they are infrequent in the distal portion.

### EMBRYOLOGICAL DEVELOPMENT.

The liver arises as a diverticulum from the ventral surface of the lower portion of the foregut immediately cranial to the opening of the gut into the yolk-sac. This diverticulum is therefore lined with entoderm. It gives off two solid buds of cells which represent the right and left lobes of the liver. The original diverticulum from the duodenum forms the bile-duct and from this are given off the cystic duct and gall bladder. This at first is a solid outgrowth but later it acquires a lumen. The opening of the bile-duct is at first in the ventral portion of the wall of the duodenum; but later, owing to the

<sup>1</sup> Huber, G. C.: Observations on Sensory Nerve Fibers in Visceral Nerves, and on their Modes of Terminating, *Jour. Compar. Neur.*, 1900, **10**, 135.

<sup>2</sup> Lütken's, U.: *Aufbau und Funktion der Extrahepatischen Gallenwege*, 1926, F. C. W. Vogel, Leipsig.

rotation of the gut, it is carried to the position which it occupies in the adult. (Figs. 16 and 17.)

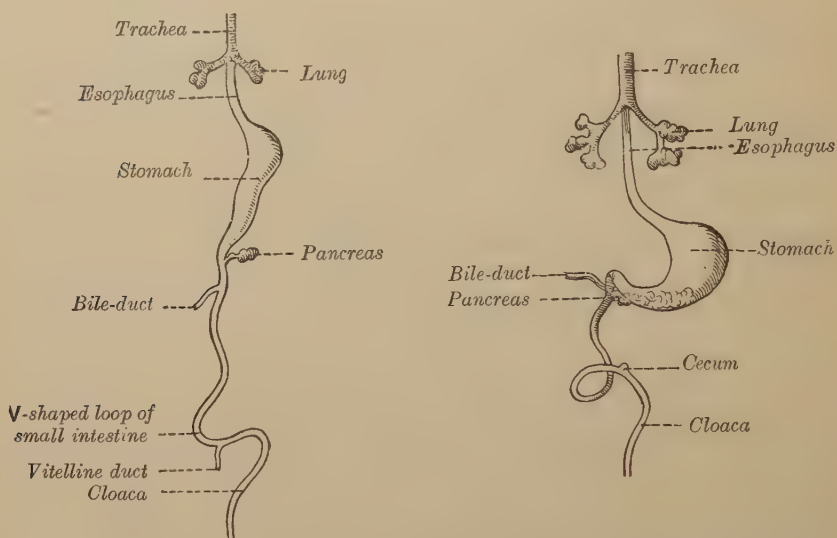


FIG. 16.—Front view of two successive stages in the development of the digestive tube. (His.)

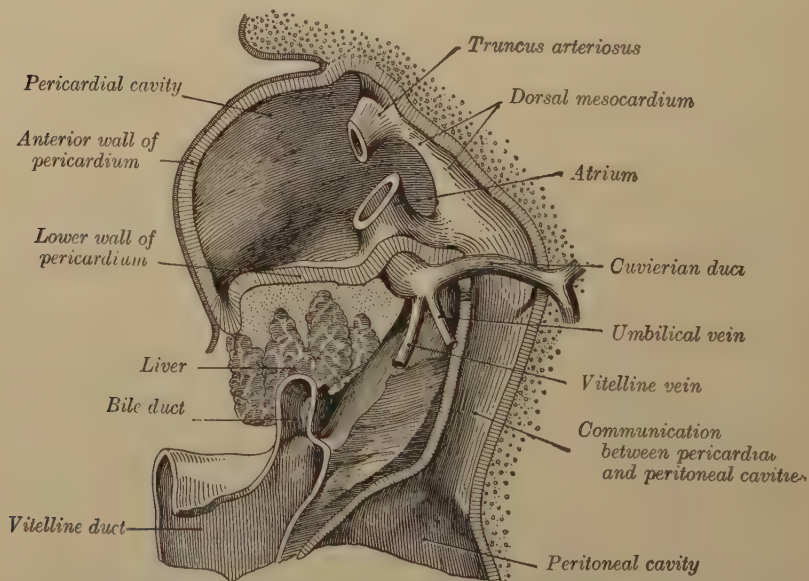


FIG. 17.—Liver with the septum transversum. Human embryo 3 mm. long. (After model and figure by His.)

## ANATOMICAL VARIATIONS.

Variations from the normal anatomy of the liver, the extra-hepatic bile passages and the bloodvessels concerned are extremely common; and many of them are of great importance from a surgical standpoint.

**Liver.**—Marked abnormal lobulation has been described, resembling somewhat the sharp definition of the lobes seen in some of the

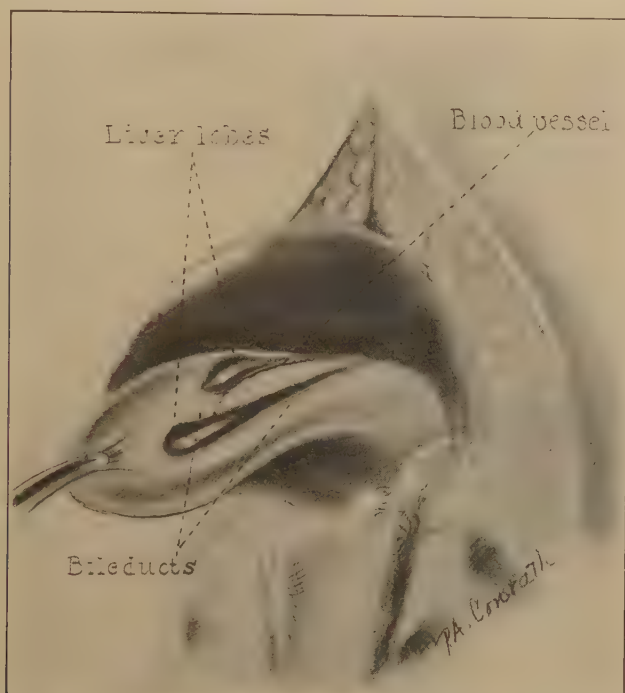


FIG. 18.—Accessory lobes of liver on the gall bladder. (Author's case.)

lower animals, as for example in the dog in which it is possible without great difficulty to remove separate lobes of the liver surgically. Abnormal variations in size of the different lobes is sometimes encountered. The left lobe has been found to be much larger than the right in some cases, and in other cases it has been found so much smaller as to be almost absent. Some of these abnormalities are pictured in Rolleston's<sup>1</sup> book.

<sup>1</sup> Rolleston, H.: Diseases of the Liver, Gall Bladder and Bile Ducts, 1905, W. B. Saunders Company.



Other abnormalities are accessory lobes and accessory livers. Rolleston quotes Peperé as having described a remarkable case in which there were innumerable small nodules of hepatic tissue or accessory livers scattered over the peritoneum and great omentum. Occasionally accessory nodules of hepatic tissue are found on the gall bladder. We have removed at operation a gall bladder on the wall of which were two accessory livers distinct from each other. (Fig. 18.) Cullen<sup>1</sup> has recently made an extensive review of this subject with the report of a case. He was able to show that the accessory liver in his case drained into an accessory bile-duct which communicated with the cystic duct. In our case also each accessory liver had its own accessory duct which joined the cystic duct. In our case the patient had a mild chronic cholecystitis without stones, and on cholecystographic examination no shadow of the gall bladder was obtained. She was completely relieved of her symptoms after the removal of the gall bladder. The location of the accessory livers on the gall bladder may be seen in the accompanying drawing. Cullen mentions several cases compiled from the literature of liver nodules in the suspensory ligament, one case in which liver tissue was embedded in a suprarenal gland, and several other instances of abnormal location of hepatic tissue. He states that he has found in the literature only one other case in which an accessory lobe of liver was found on the gall bladder.

Riedel's<sup>2</sup> lobe is a well-known deformity of the liver, first described by Riedel of Jena in 1888. It is a downward prolongation of a portion of the right lobe of the liver, occurring more often in women than in men. In some cases tight lacing is thought to be the cause of it, but in many cases it is associated with cholecystitis or with adhesions to other abdominal viscera. When felt through the abdominal wall of a patient it is often mistaken for an enlarged gall bladder or kidney.

**Gall Bladder.**—In some animals the gall bladder is normally absent. For example, no gall bladder is present in the horse, the deer, the rat, the pocket gopher, the dove and the peccary. Much comment has been aroused as to why the mouse should have one but not the rat, the pocket gopher but not the striped gopher, the hog and wild boar but not the peccary. Woods Hutchinson<sup>3</sup> states that

<sup>1</sup> Cullen, T. S.: Accessory Lobes of the Liver: An Accessory Hepatic Lobe Springing from the Surface of the Gall Bladder, *Arch. Surg.*, 1925, **11**, 718.

<sup>2</sup> Riedel: Erfahrungen über die Gallensteinkrankheit mit und ohne Icterus, 1892, Berlin, A. Hirschwald.

<sup>3</sup> Hutchinson, Woods: Is the Gall Bladder as Useless as it is Dangerous? *Med. Rec.*, 1903, **63**, 770.



in the giraffe the gall bladder is sometimes present and at other times absent. Sweet,<sup>1</sup> however, has found that in the horse there are many saccules, barely visible to the naked eye, somewhat like diverticula, projecting from the hepatic ducts. (Figs. 19 and 20.)



FIG. 19.—Parietal sacculi of horse, which normally has no gall bladder. (From Sweet after Sappey.)

He has suggested that perhaps these have a function of a gall bladder. Complete absence of the gall bladder in the human is of very rare occurrence, although the condition has been described. We once observed a case at operation on a negress in which careful dissection

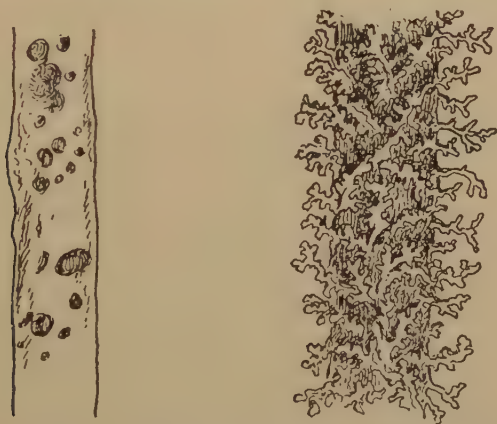


FIG. 20.—Parietal sacculi of normal dog. Same in a dog after cholecystectomy. (After Sweet.)

of the common, the hepatic and the right and left hepatic ducts failed to reveal any evidence at all of either a gall bladder or cystic duct.

<sup>1</sup> Sweet, J. E.: The Gall Bladder: Its Past, Present and Future, *Internat. Clin.* 1924, 1, 187.

A very interesting study of the extra-hepatic biliary apparatus in both the rat and the mouse has been made by McMaster.<sup>1</sup> This is of special importance because of the absence of a gall bladder in the former animal and its presence in the latter. He has found that the rat does not possess any concentrating mechanism in the extra-hepatic ducts which is analogous to that of the normal gall bladder. He did find, however, that the bile of the rat contains on an average eight times as much pigment as does the hepatic bile of the mouse. He also found that the bulk of bile secreted per gram of liver weight is identical in both animals. Higgins<sup>2</sup> has confirmed this finding of McMaster's concerning the greater concentration of pigment in the rat bile. He suggests that in this animal without a gall bladder an intra-hepatic concentration may occur in a plexus of bile-ducts around the portal vein which he found in the rat. This observation and suggestion is in line with that of Sweet's, quoted above, with reference to the saccules along the hepatic ducts of the horse, another animal which normally has no gall bladder.

**Biliary Glands or Crypts.**—With reference again to the observation of Sweet, it should be stated that, as he says, the ancient anatomists recognized similar saccules issuing from the larger intra-hepatic ducts. These have been given many names, the most common of which probably is that of biliary glands or glandules. Poirier and Charpy<sup>3</sup> discuss them as follows: "The biliary glands are relatively voluminous on the large branches of division of the hepatic canal where their dimensions vary from 0.5 to 1 mm. They affect the type of composite utricular glands. Their excretory canal subdivides itself into a certain number of branches diverging at right angles which terminate in little lobulated formations each composed of five or six vesicles whose diameters reach from 90 to 100 microns. The orifices of the excretory ducts, visible to the naked eye on the opened bile-ducts, measure about 0.5 mm. They did not escape the observation of the ancient anatomists, and Kiernan has described them as the pores of glandular follicles. The large bile ducts present also rudimentary formations analogous to those which we have studied on the ducts of smaller caliber.

"All the glands or glandules are constructed on the same type; they present a wall of connective tissue in which is found a rich capillary network and they are lined by a simple cylindrical epithe-

<sup>1</sup> McMaster, P. D.: Do Species Lacking a Gall Bladder Possess its Functional Equivalent? *Jour. Exper. Med.*, 1922, **35**, 127.

<sup>2</sup> Higgins, G. M.: The Biliary Tract of Certain Rodents With and Those Without a Gall Bladder, *Anat. Rec.*, 1926, **32**, 89.

<sup>3</sup> Poirier and Charpy: *Loc. cit.*, vol. 4, p. 768.

lium analogous to the epithelium which covers all the biliary passages. Legros and Ranvier have insisted on the fact that this epithelium does not show glandular differentiation, and Renault has proposed to designate these pseudoglands under the name of crypts. E. H. Weber likened them to aberrant vessels, while Kölliker and Beale considered them as reservoirs of bile. But the rich vascular network and the presence of cholesterin in their epithelium permits one to suppose that they furnish certain elements of the biliary secretion. Their constancy in the animal series even makes one think that they play a rather active rôle in this secretion. One must, however, avoid exaggerating their importance—the form and the dimensions of the biliary glands vary according to the animal species. Their number is sometimes so great that it is very difficult, as Sappey has observed, to see the wall of the bile duct.”

**Vasa Aberrantia.**—Also because of their bearing upon the points discussed above, mention should be made of the poorly understood structures which are sometimes called *vasa aberrantia* or aberrant ducts. The description of them given by Poirier and Charpy<sup>1</sup> is so concise and clear that their account is quoted as follows:

“When, after a good injection of the biliary passages, one examines carefully the surface of the liver, it is not rare to observe, under the fibrous envelope, some ducts which subdivide and anastomose with each other without even coming into relationship with any lobules. These special ramifications of the biliary passages were well known to Ferrein (1753) who saw them particularly in the triangular ligament. In turn taken for lymphatics or for blood capillaries (J. Müller), they have been well studied by E. H. Weber (1842) who determined their true nature and gave to them the name of *vasa aberrantia*. These aberrant ducts recall, in fact, by their structure that of the biliary passages and are, like them, composed of a wall with a cylindrical epithelium. They ramify into canals more and more slender, anastomose in a network and terminate in blind extremities, sometimes distended into ampullæ. The aberrant ducts, in general, have a yellow color and are provided with numerous glands, sometimes atrophied and deformed, sometimes, on the contrary, markedly hypertrophied.

“The majority of authors consider the *vasa aberrantia* as proliferating branches of the primitive tubular liver, arrested in their development, which have not given birth at their extremity to hepatic parenchyma. Sappey holds a slightly different opinion;

<sup>1</sup> Poirier and Charpy: Loc. cit., vol. 4.

to him, the aberrant vessels represent superficial parts of the liver whose lobules must have atrophied, at the same time that the excretory ducts took on a considerable development. He justifies this hypothesis by arguing that one never sees aberrant vessels either in the fetus or in the infant, that one encounters them in adults after a certain age, and that finally they are frequent in the aged. Such facts are not absolutely exact. Several times we have seen *vasa aberrantia* well developed on the liver of the fetus at term.

"In their work on the evolution of the human liver, Toldt and Zuckerkandl (1875) strove to specify the places where they are most often found. The aberrant vessels observed by Ferrein in the left triangular ligament are those which have been the first described. Ferrein and Kiernan would have followed them right up to the inferior surface of the diaphragm, whereas Theile has met them most often on the surface of the liver in this region, but he has never seen them insinuate themselves between the two leaves of the triangular ligament. In general they present themselves in the form of eight or ten tubes anastomosed in a network whose transverse diameter measures from 40 to 50 microns in a length of 1 mm. Another place of election of the aberrant ducts is situated behind the Spigelian lobe, at the level of the bridge of fibrous tissue which passes behind the inferior vena cava, in the hepatic region of which one is almost sure to find them. One also meets them very often around the gall bladder and in the furrow of the umbilical vein. Sappey has also found them at the level of the attachment of the suspensory ligament and along the sharp border of the liver. Perhaps also some aberrant ducts exist in the interior of the liver at the level of the portal spaces, as in the neighborhood of the hilum, but they are never in direct relationship with the dividing branches of the portal vein.

"The aberrant vessels are not limited to the human species, and the majority of the mammals possess examples of them. Barpi and Tarnello (1901) have described them in the solipeds even in the central tendon of the diaphragm and in the adventitia of the portal vein. Their constancy in the higher vertebrates just as the presence in their interior of a mucous and yellowish liquid would seem to justify up to a certain point the opinion of those authors who assign to them an active rôle in the biliary secretion. E. H. Weber likens them to true glands annexed to the bile-ducts; it might be possible to consider them as reservoirs in which the bile accomplishes its elaboration, when digestion is not taking place or when the bile is not flowing into the intestine."



**Duplication of Gall Bladder.**—Of greater interest because of greater frequency of occurrence are those abnormalities which are concerned with the duplication of the gall bladder. Boyden<sup>1</sup> has made the most extensive study of this subject that has been made, and he has recently brought the whole matter up to date. In a study based on examinations of 10,000 domestic mammals (equal numbers of cats, calves, sheep and pigs) and upon reports covering approximately 19,000 cadavers and hospital patients, he has found 456 cases of congenital duplication of the gall bladder. The incidence of cases varied with the different species as follows: 1 in 8 cats; 1 in 28 calves; 1 in 85 lambs and sheep; 1 in 198 pigs; 1 in 3000 to 4000 human beings. As compared with these other mammals, therefore, the human is remarkably free from this abnormality. Boyden states: "A comparative study of these anomalies in adults and embryos demonstrates trends of variation characteristic of each species, although several types of variation may be present in a given species or in a given individual. Four embryonic types of accessory gall bladder are differentiated, the last three of which are presented here for the first time. These comprise: (1) Cleft gall bladders—forms which originate by initial subdivision of the primary cystic diverticulum of the embryo (chiefly characteristic of cats); (2) diverticular bladders—distinct vesicles or subordinate lobes, arising as buds from the neck of the embryonic gall bladder and usually associated with cyst-hepatic ducts (chiefly characteristic of ungulates); (3) ductular bladders—supernumerary vesicles derived from either hepatic, cystic, or common bile-ducts (chiefly characteristic of human gall bladders, but present also in cats); (4) trabecular bladders—vesicular out-growths of liver trabeculae bordering the fossa vesicae felleae (rare anomalies found as yet only in cattle, sheep, and possibly cats, but undoubtedly related to aberrant cysts found in the tunica adventitia of the human gall bladder)." Boyden has also described for the first time the occurrence of a temporary enlargement on the biliary-duct system—the hepatic antrum—which was common to all vertebrates examined. He thinks that in man this may furnish an anatomical basis of interpretation of the condition of so-called idiopathic enlargement of the ductus choledochus. This condition, also sometimes known as congenital cyst of the common bile duct, has been recently described and the literature brought up to date

<sup>1</sup> Boyden, E. A.: The Accessory Gall Bladder. An Embryological and Comparative Study of Aberrant Biliary Vesicles Occurring in Man and the Domestic Animals, *Am. Jour. Anat.*, 1926, **38**, 177.



by Morley.<sup>1</sup> It will be mentioned again later in other sections of this book.

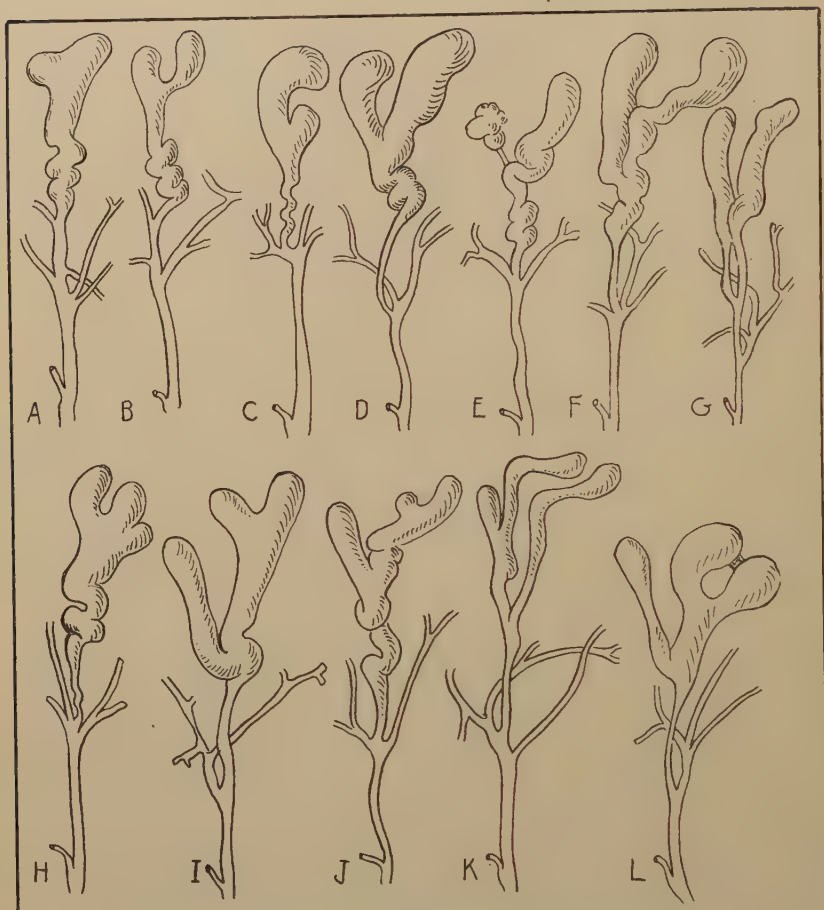


FIG. 21.—Selected examples of the vesica fellea divisa in cats, resulting from initial subdivision of the embryonic primordium. *A* and *B*, fundus slightly cleft; *C* to *F*, deeply cleft; *E*, right lobe represented by cyst; *G*, Y-shaped type of double gall bladder; *H* to *L*, trilobed gall bladders. (After Boyden.)

The accompanying illustrations show common varieties of divided and of double gall bladder as found by Boyden. (Figs. 21, 22 and 23.)

It is interesting that the old Jewish Talmudic law takes cogni-

<sup>1</sup> Morley, John: Congenital Cyst of the Common Bile Duct: With Report of Two Cases, *British Jour. Surg.*, 1922, **10**, 413.

zance of some of the abnormalities of the gall bladder in considering whether the food from a certain animal is "kosher" (suitable for eating) or "terefah" (unfit for food). From the passages quoted by

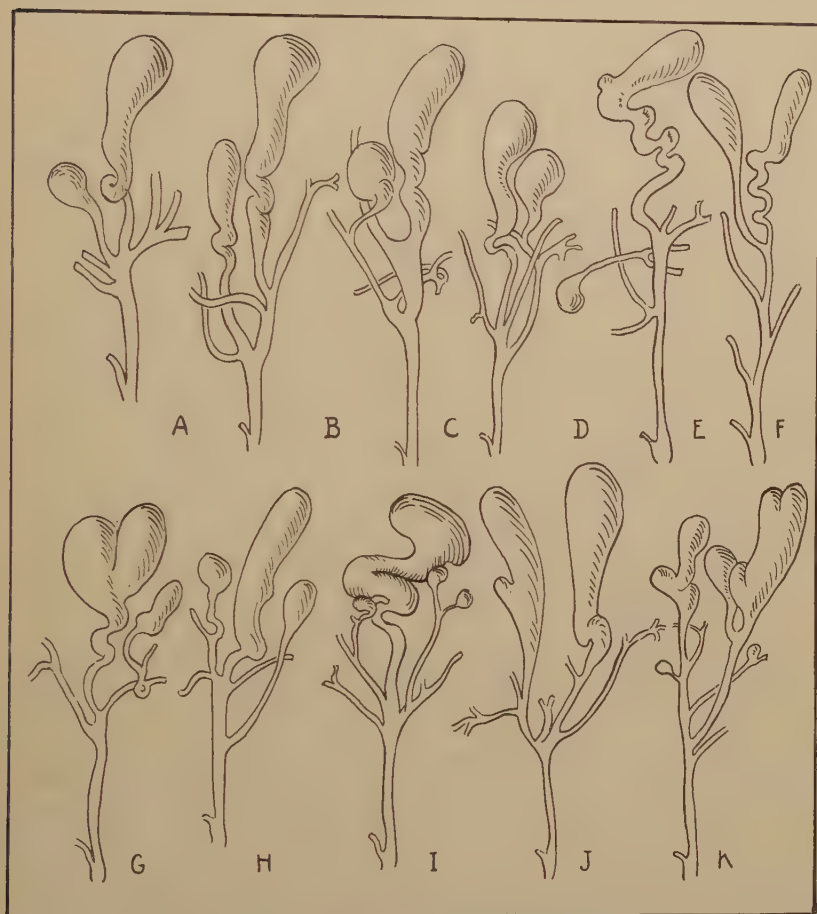


FIG. 22.—Selected examples of the vesica fellea duplex in cats. *A* to *E*, ductular type, in which the accessory vesicle represents an independent outgrowth of the hepatic ducts; *F*, Y-shaped type of double gall bladder, representing either a very deeply cleft gall bladder or a supernumerary vesicle originating as an outgrowth of the cystic duct; *G* and *J*, pseudomultiplex; *H*, *I*, *K*, true multiplex vesicles. (After Boyden.)

Boyden from Joseph Caro's sixteenth century "Shulhan 'Aruch," the final and authoritative codification of the Talmudic law, accepted by all orthodox Jews of whatever nationality, the following are taken:

"If the gall bladder has been removed by hand, or if it is missing, the animal is terefah.

"If the gall bladder is absent or missing, then the liver is to be cut up criss-cross and tasted with the tongue (to see if the bile is absent). If it tastes bitter it is kosher, if it does not taste bitter it shall be broiled on coals and tasted again; if then there is a bitter taste, it is kosher; if not, it is terefah.

"If two gall bladders are found, the animal is terefah, for it is the same as if it were missing. If it is one and appears like two, then an opening is made (through the wall); if the gall pours from one into the other, the two gall bladders are one and the animal is kosher; if not, proving them two, it is terefah.

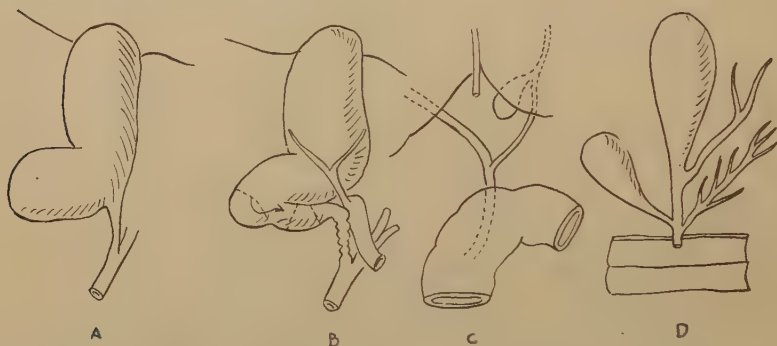


FIG. 23.—Illustrating certain types of human anomalies. *A*, gall bladder in a cadaver, simulating a vesica fellea divisa; *B*, same bladder after inflation and dissection; *C*, Kehr's case of atypically placed gall bladder (interpreted by Boyden as an aberrant vesicle of ductular origin, associated with congenital absence of the definitive gall bladder); *D*, Blasius's case of vesica fellea duplex, 1674 (the only published figure of the human double gall bladder which shows the termination of the two cystic ducts). The smaller vesicle may be a pancreatic bladder, as it enters the choledochus just above the entrance of the pancreatic duct. (After Boyden.)

"If the two gall bladders are distinctly separate, but become one where they meet in the liver, for a distance as great as the width of a finger, the animal is kosher, even if the contents of one does not pour into the other; similarly, if they begin as two but join into one at the end, the animal is kosher.

"There are some birds which have no gall bladders, such as doves and pigeons, but these should not on this account be made terefah so long as this is characteristic of the entire species. (Commentary by Kimbi, early thirteenth century: "Some animals have no gall bladder at all; some have gall bladders on the intestines, as doves, quail and the canary; some have the gall bladder in the belly and some have it in their ears.")

"If hard things are found in the gall bladder which are like the pits of dates, without sharp edges, the animal is kosher. But if the edges are sharp, as in the pits of olives, the animal is terefah, it being assumed that the pit has perforated the gall bladder in entering; the reason why the perforation is not visible is because it is healed over with skin."

**Variations in the Ducts and Bloodvessels.**—Variations in the arrangement of the ducts and of the bloodvessels have been exhaustively studied both by Eisendrath<sup>1</sup> and by Flint.<sup>2</sup> A knowledge of at least the most frequent of these variations is of the greatest importance to the surgeon. I shall quote largely from their published articles. Eisendrath's results were obtained from a study of 100 dissections at necropsy, and Flint's from a study of 200 post-mortem dissections.

Eisendrath's studies were made chiefly of the arrangement of the ducts and but little attention was devoted to the arrangement of the arteries. On the other hand, Flint's studies concern the arrangement of the arteries as well. Eisendrath divides the types of arrangement of the ducts into three classes: (1) Those in which the cystic duct joins the hepatic duct at an angle; (2) those in which the cystic duct runs parallel with the hepatic duct for a variable distance; (3) those in which the cystic duct winds spirally around the hepatic duct before uniting with it. The latter two types are of particular interest. In the parallel type sometimes the cystic duct runs parallel with the hepatic duct for only a relatively short distance, but in other cases he found them running parallel almost to the ampulla. In the spiral type the cystic duct winds around either the front or behind the hepatic duct before entering it to form the common duct. Thus the cystic duct can describe one-quarter, one-half, three-quarters, or a complete spiral around the hepatic duct. He found in 75 per cent of cases the angular type of union of the ducts, in 17 per cent the parallel type and in 8 per cent the spiral type. These figures closely agree with the previous findings of Descomps.<sup>3</sup>

Flint comments on what the anatomical text-books regard as the normal arrangement, namely, that "the length of the supraduodenal

<sup>1</sup> Eisendrath, D. N.: *Anomalies of the Bile Ducts and Bloodvessels*, Jour. Am. Med. Assn., 1918, **71**, 864.

<sup>2</sup> Flint, E. R.: *Abnormalities of the Right Hepatic, Cystic, and Gastro-duodenal Arteries, and of the Bile Ducts*, British Jour. Surg., 1922, **10**, 509.

<sup>3</sup> Descomps, P.: *Les vaisseaux sanguins et les voies biliaires dans le bile du foie*, Bull. de la Soc. Anat., 1910, **85**, 323; *Recherches d'anatomie chirurgicale sur les artères de l'abdomen, le tronc coeliaque*, Paris, G. Steinheil, 1910.



part of the common bile-duct varies with the level of the duodenum and the point at which the cystic and common hepatic ducts join; the average length for this part of the duct is held to be about one-third of the whole length of the common duct." Then he states that "though it is true that the cystic and common hepatic ducts do come together at such a point as to give an average of lengths as stated, they do not unite here. Almost always they are merely bound together by fibrous tissue, and by dissection it is possible to separate them from each other for a few millimeters to as much as 4 cm. or more. The most common point, according to my observations, at which union actually occurs is within 1 cm. of the upper border of the duodenum." In 28 cases (nearly 15 per cent) he found no supraduodenal common duct at all; in these cases the union occurred at a point anywhere from behind the upper border of the duodenum to the part embedded in the pancreas, and in 3 cases the only representative of the common duct was that part which lies in the wall of the duodenum. He mentions also the comparative frequency of the spiral relationship of the cystic duct to the hepatic duct, already commented on by Eisendrath.

Accessory bile-ducts received from Flint one of the first extensive studies that have been made on these surgically important structures. The much debated question of whether or not to institute drainage after cholecystectomy is concerned largely with the possibility of the escape of bile. Most surgeons have regarded the occasional postoperative escape of bile as having been due to the slipping of the ligature from the stump of the cystic duct, due perhaps to insecure ligation. A knowledge, however, of some of the accessory ducts which may be encountered will convince anyone that occasionally such ducts will of necessity be cut across during the removal of the gall bladder. If recognized they may be ligated. If not, bile is very likely to escape from the cut end for several days or even longer. We have often seen accessory ducts of varying size during the course of operations on the gall bladder, some of which we ligated separately to avoid a postoperative escape of bile.

Flint states that he saw 29 examples of accessory bile-ducts in his 200 dissections (almost 15 per cent). Because of his careful study of this question we quote him *in extenso*. "All of them are accessory right hepatic ducts. The duct leaves the liver at the extreme right end of the portal fissure, and, lying at first on a rather deeper plane than the cystic duct, joins the extra-hepatic ducts anywhere between the junction of the right and left hepatic ducts and the point at which the cystic duct opens into the main duct.



It usually has the same relation to the right hepatic artery as the normal ducts—that is, the artery passes behind the duct.

“I have classified these accessory ducts into three types, according to the level at which they enter the main duct. This is done from a surgical rather than an anatomical standpoint.

“1. The junction occurs in the upper half of the common hepatic duct or in the right hepatic duct. There are 9 of these. In this type the union is so high up that the duct is unlikely to be of surgical importance.

“2. The junction occurs in the lower half of the common hepatic duct. There are 9 cases in this class also. The union is so near that of the cystic and common hepatic ducts as to be definitely in the field of a cholecystectomy operation.

“3. The junction is at the union of cystic and common hepatic ducts. There are 10 of these cases. The junction is usually in the acute angle of the cystic and common ducts, but may be in the extreme lower end of the cystic duct, or in the extreme lower end of the common hepatic duct. In any case it is difficult to see how the duct could be avoided while clamping the cystic duct unless its presence had been previously detected.

“In one specimen the accessory duct leaves the right hepatic duct and enters the cystic duct, and of course must be cut during cholecystectomy.

“The size of these accessory ducts varies. The smallest is only large enough to admit a good-sized bristle. The largest is as big as the right hepatic duct. The commonest size is about half-way between these limits; that is to say, it is quite a considerable duct.” (Figs. 24 to 53.)

Perhaps another anatomical variation is the condition known as congenital obliteration of the ducts. The first comprehensive account of this condition was given by John Thomson<sup>1</sup> of Edinburgh in 1892. It is possible that in some cases of this condition, canalization of the lumens of the ducts has failed to take place, although in many cases there seems to be evidence that an intra-uterine inflammatory process has closed them. In extreme cases the entire extra-hepatic biliary system is represented merely by a fibrous cord. In others, only a part of the system is affected, often the common duct near the duodenum. Sometimes the common duct is patent but the right and left hepatic ducts are non-patent.

<sup>1</sup> Thomson, John: Congenital Obliteration of the Bile Ducts, *Edinburgh Med. Jour.*, 1892.

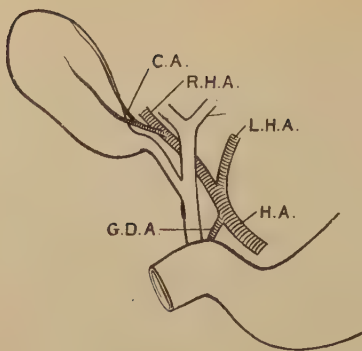


FIG. 24

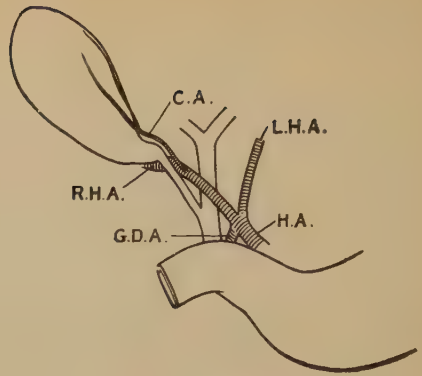


FIG. 25

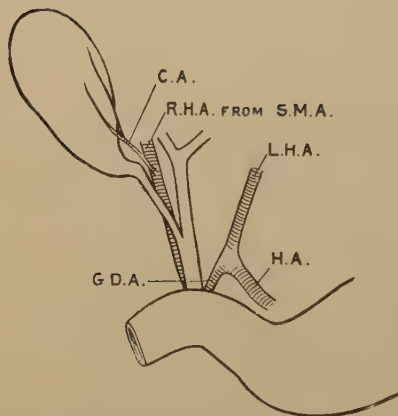


FIG. 26

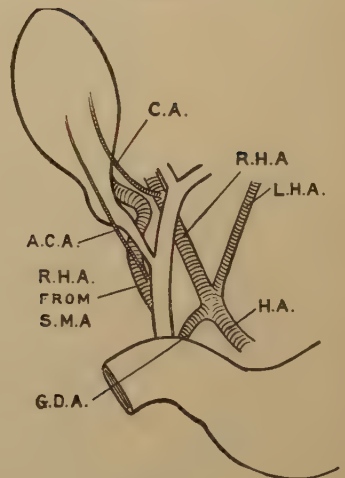


FIG. 27

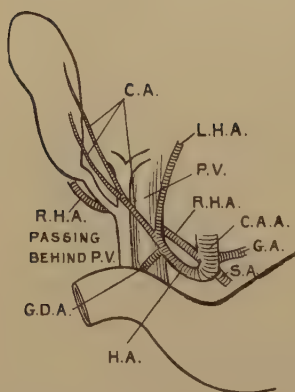


FIG. 28

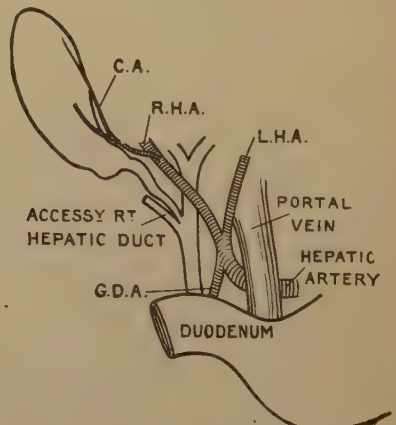


FIG. 29

FIGS. 24 to 53.—Diagrams illustrating various abnormalities in the arteries and bile-ducts met with in gall-bladder surgery. C.A., cystic artery; G.D.A., gastroduodenal artery; H.A., hepatic artery; L.H.A., left hepatic artery; R.H.A., right hepatic artery; S.M.A., superior mesenteric artery; A.C.A., accessory cystic artery; P.V., portal vein; C.A.A., celiac axis artery; G.A., gastric artery; S.A., splenic artery; R.H.D., right hepatic duct; S.P.D.A., superior pancreatico-duodenal artery; C.D., cystic duct. (After Flint, *British Journal of Surgery*.)

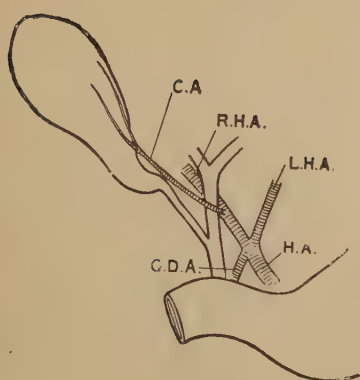


FIG. 30

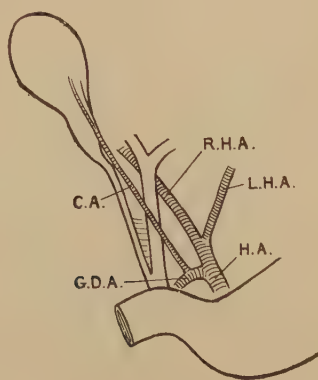


FIG. 31

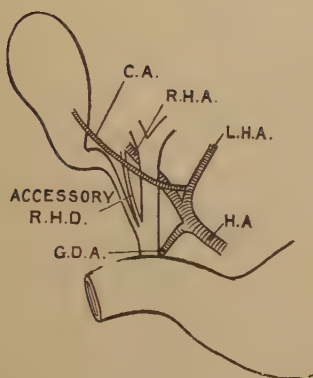


FIG. 32

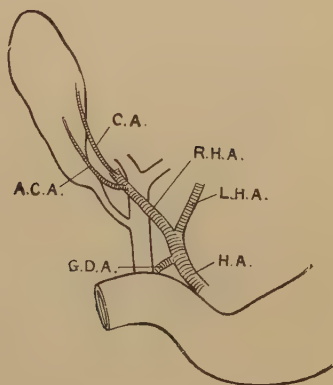


FIG. 33

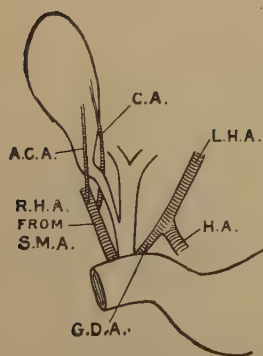


FIG. 34

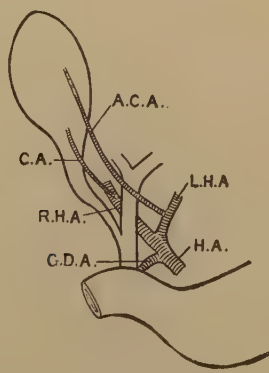


FIG. 35

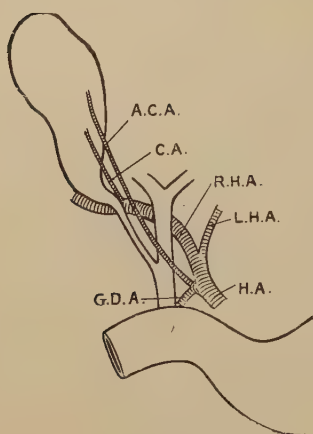


FIG. 36

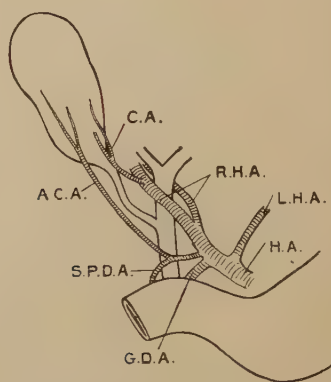


FIG. 37

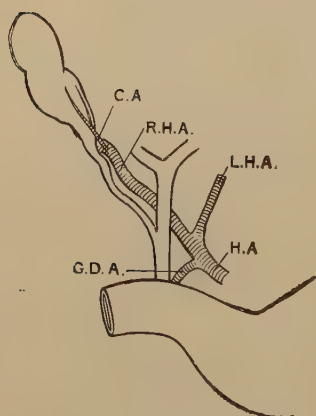


FIG. 38

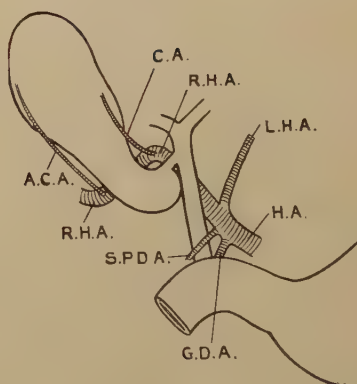


FIG. 39

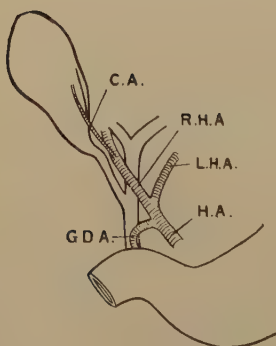


FIG. 40

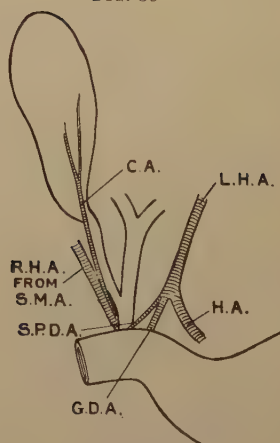


FIG. 41

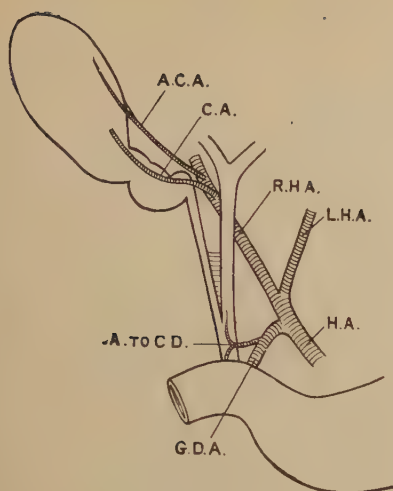


FIG. 42

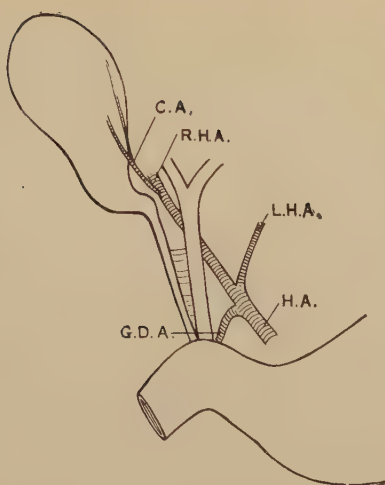


FIG. 43

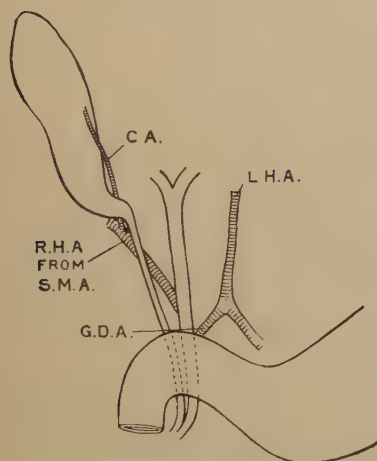


FIG. 44

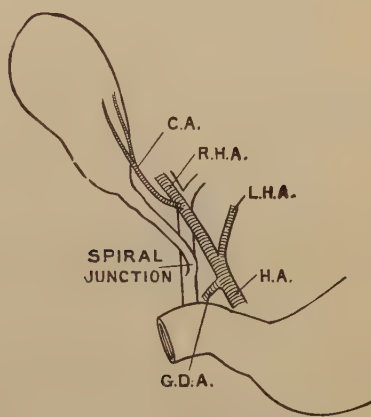


FIG. 45

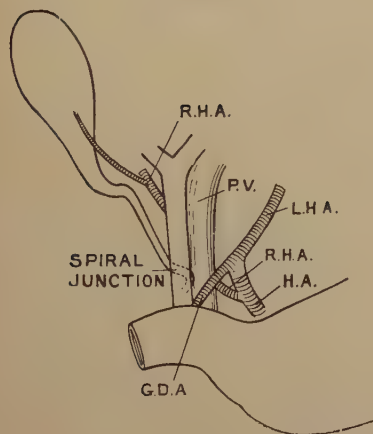


FIG. 46

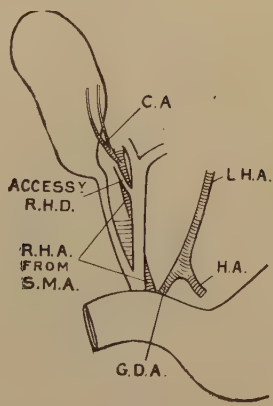


FIG. 47



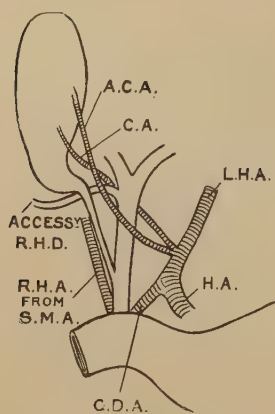


FIG. 48

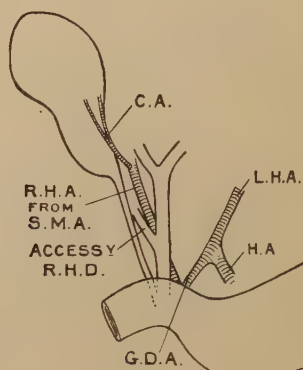


FIG. 49

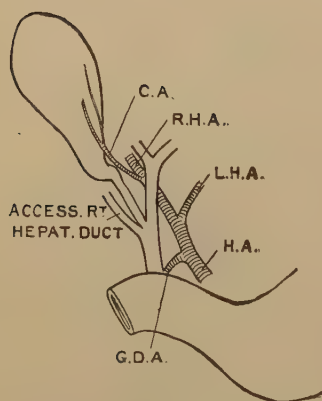


FIG. 50

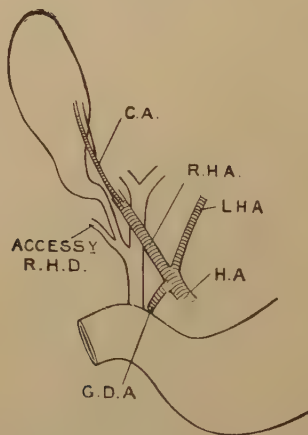


FIG. 51

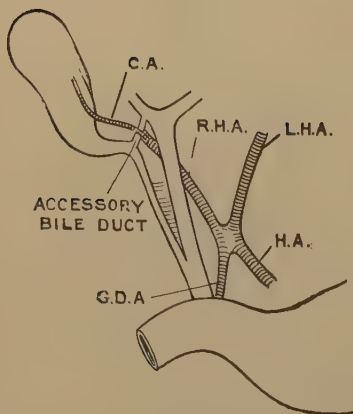


FIG. 52

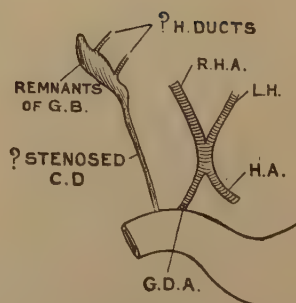


FIG. 53

As might be expected, this condition of congenital obliteration of the ducts manifests itself in early infancy; and in the severe cases life cannot continue for more than a few weeks or months. The whole question is discussed more extensively later in the section dealing with the bile-ducts.

The arrangement of the arteries in the neighborhood of the gall bladder is about as variable as that of the ducts. Occasionally the *right hepatic artery* arises from the aorta, the renal artery, the gastric, or the inferior mesenteric artery. In Flint's series of 200 dissections this artery arose from the main hepatic trunk in 158 cases. In 136 cases it passed behind the common hepatic duct and in 25 in front of it. In 42 cases it arose from the superior mesenteric artery, in all of which cases it passed behind the common duct. In 7 cases there were two right hepatic arteries, one from the hepatic trunk and one from the superior mesenteric. In 2 cases there were two right hepatics both from the main hepatic, one passing in front of, and the other behind, the common hepatic duct. In 4 cases in addition to passing behind the ducts, the main hepatic or the right hepatic artery also passed behind the portal vein. In 25 cases the location of this artery was such as to be very liable to injury during an operation of cholecystectomy.

The *cystic artery* arose from the right hepatic in 196 cases of the 200; in 3 from the left hepatic, and in 1 from the gastro-duodenal artery. In 32 cases it passed in front of the common hepatic duct, and in 168 it arose just to the right side of the common hepatic duct or behind it. The former was much the more common.

An *accessory cystic artery* was present in 31 cases. It arose from the right hepatic in 16 cases, from the left hepatic in 3, from the gastro-duodenal in 11, and from the superior pancreatico-duodenal in 1 case. It invariably crossed in front of the bile-ducts.

Flint has also studied the artery which sometimes gives rise to troublesome hemorrhage when the common duct is opened. This artery is not described in the text-books of anatomy, but Flint found it of frequent occurrence. It arises from the hepatic artery low down, or from the superior pancreatico-duodenal, or from the gastro-duodenal, and runs a rather tortuous course along the anterior surface of the duct. It may be the superior pancreatico-duodenal itself, when this vessel comes off higher than usual. The gastro-duodenal artery also in a small percentage of cases forms a curve in front of the lower supraduodenal part of the common duct and might be wounded in opening the common duct.

**Variations in Attachment of Gall Bladder to Liver.**—Normally, the gall bladder is held rather closely against the under surface of the liver by attachments of connective tissue. This attachment is subject to great variation. During childhood and up to about the age of puberty there is but little variation in different subjects or in the two sexes. Later in life, however, the variations become strikingly revealed. In some instances the gall bladder is attached to the liver by a long mesentery which permits very great mobility and ptosis. Extreme ptosis of the gall bladder is usually found associated with a more or less general ptosis of the abdominal organs. As contrasted with extreme ptosis of the gall bladder there is the condition in which it is held tightly against the under surface of the liver by unyielding connective tissue. Between these two extremes one meets with all possible gradations. Lützens<sup>1</sup> has made a special study of these different types, and he concludes that the ptotic type represents about 20 per cent of all subjects. This matter is again discussed in the chapter on Radiology.

<sup>1</sup> Lützens, U.: *Aufbau und Funktion der Extra-hepatischen Gallenwege*, 1926, F. C. W. Vogel, Leipsig.

## CHAPTER II.

### PHYSIOLOGY OF THE GALL BLADDER.

**Introduction.**—The functional activities of the gall bladder have long remained obscure in spite of a great amount of study of the subject by able investigators. Though at present there remains much to be learned regarding the gall bladder, and, although there is not common agreement concerning some of the activities of the organ, the situation has been greatly clarified by the development of cholecystography, which is a method permitting roentgenological visualization of the gall bladder. The method has facilitated the insight into both normal and abnormal functions of the gall bladder in man and animals. The reader is reminded that all facts true of the gall bladder in animals are not necessarily true of the gall bladder in man.

In the succeeding attempt at the evaluation of the present knowledge concerning the functions of the gall bladder, stress will be laid upon the newer information obtained directly or indirectly as a result of roentgenological study of the vesicle. However, much of the work preceding the advent of this method is of fundamental value and will be discussed.

### EXPERIMENTAL CHOLECYSTOGRAPHY.

The discovery of a new method of roentgenological examination of the gall bladder was reported in 1924 by two of us.<sup>1</sup> On the basis of the preceding work of Abel and Rowntree,<sup>2</sup> who had shown that the phenolphthaleins, as a class, were largely excreted in the bile, we found that when phenolphthalein, containing either iodine or bromine, was injected intravenously into animals or man, it also was excreted in the bile and a sufficient concentration of the halogen was obtained in the gall bladder to cast a shadow on a film when exposed to the roentgen-ray. The name "cholecystography"

<sup>1</sup> Graham, Evarts A. and Cole, W. H.: Roentgenological Examination of the Gall Bladder, Preliminary Report of a New Method Utilizing the Intravenous Injection of Tetrabromphenolphthalein, Jour. Am. Med. Assn., 1924, **82**, 613.

<sup>2</sup> Abel, John J. and Rowntree, L. G.: On the Pharmacological Action of Some Phthaleins and their Derivatives, with Especial Reference to their Behavior as Purgatives, Jour. Pharmacol. and Exper. Ther., 1909-1910, **1**, 231.

has been applied to the visualization of the gall bladder by this method, and the exposed roentgen-ray films are called "cholecystograms."

Much experimental work was done by us<sup>1</sup> with the phenolphthaleins and other compounds. The results of these experiments were reported in part in the Leonard Research Prize Essay of 1925.<sup>2</sup>

The first experiments were made with the sodium salts of tetraiodophenolphthalein and tetrabromphenolphthalein. The calcium salts were then tried but were soon replaced by the more soluble sodium salts. Shadows of the gall bladder were obtained after intra-venous, oral and rectal administration of these substances. These early experiments of ours<sup>3</sup> with cholecystography were with tetraiodophenolphthalein, but because of impurities in the samples obtained at that time, the early clinical application of the method was made with sodium tetrabromphenolphthalein. Later, Milliken and Whitaker,<sup>4</sup> apparently having obtained a good sample, concluded that tetraiodophenolphthalein is superior to tetrabromphenolphthalein for clinical use. Their report was published practically simultaneously with one of ours<sup>5</sup> in which we reported the resumption of the use of tetraiodophenolphthalein after having secured a more highly purified product. Since that time, we<sup>6</sup> have concluded that the isomer of this substance, namely, sodium phenoltetraiodophthalein, is the best substance available at present for cholecystography, and we are using it in our experimental and clinical studies of the gall bladder.<sup>7</sup>

Other substances are capable of making the gall bladder opaque to the roentgen-ray after intravenous injection. In attempting to find the ideal drug for this and other purposes, we have studied

<sup>1</sup> Graham, Evarts A., Cole, W. H. and Copher, Glover H.: Cholecystography: An Experimental and Clinical Study, Jour. Am. Med. Assn., 1925, **84**, 14.

<sup>2</sup> Graham, Evarts A., Cole, W. H. and Copher, Glover H.: Cholecystography: Its Development and Application, Leonard Research Prize Essay, Am. Jour. Roentgenol. and Rad. Ther., 1925, **14**, 487.

<sup>3</sup> Graham, Evarts A., Cole, W. H. and Copher, Glover H.: Visualization of the Gall Bladder by the Sodium Salt of Tetrabromphenolphthalein, Jour. Am. Med. Assn., 1924, **82**, 1777.

<sup>4</sup> Milliken, G. and Whitaker, L. R.: The Clinical Use of Sodium Tetraiodophenolphthalein in Cholecystography, Surg., Gynec. and Obst., 1925, **40**, 646.

<sup>5</sup> Graham, Evarts A., Cole, W. H. and Copher, Glover H.: Cholecystography: The Use of Sodium Tetraiodophenolphthalein, Jour. Am. Med. Assn., 1925, **84**, 1175.

<sup>6</sup> Graham, Evarts A., Cole, W. H., Copher, Glover H. and Moore, Sherwood: Cholecystography: The Use of Phenoltetraiodophthalein, Jour. Am. Med. Assn., 1926, **86**, 1899.

<sup>7</sup> The sodium salts of tetraiodophenolphthalein and of phenoltetraiodophthalein are marketed by the Mallinckrodt Chemical Works of St. Louis under the names of Iodeikon and Iso-iodeikon respectively. These are the products which we employ as a routine.



forty-seven substances. (See chapter on Radiology.) A considerable number of possibilities that will produce cholecystograms exist, and it is therefore entirely possible that in the future some other substance than phenoltetraiodophthalein may be preferable to any of those so far used.

Sodium phenoltetraiodophthalein, which is being used most extensively by us at the present time, is fairly representative of the class of substances which produce cholecystograms. It contains approximately 60 per cent of iodine by weight, the iodine or the bromine being in each instance the substance which is opaque to the roentgen-ray.

Phenoltetraiodophthalein may be administered by mouth or intravenously. It is excreted in the bile by the liver shortly after intravenous injection, and diverted into the gall bladder by the action of the sphincter of the common duct, if the subject is fasting. Once inside the gall bladder, the bile and iodine become more concentrated, due to the absorption of water by the wall of the viscus. It is during this period of about twenty-four hours that shadows may be procured on films by exposing the gall bladder to roentgen-rays. The iodine is removed from the normal gall bladder as it empties, and with it goes the opacity of the organ to the roentgen-ray. It is evident from this brief description that there is normally a cycle of filling and emptying of the gall bladder, after the administration of a suitable substance, a process which may be visualized radiographically.

Clinical application of these facts was very soon made,<sup>1</sup> and criteria were established for the diagnosis of the shadows produced by normal and pathological gall bladders in the human. The method has also been used extensively, as will be seen later, in the study of the physiology of the gall bladder.

### THE FILLING OF THE GALL BLADDER.

Bile, continuously secreted by the liver at varying rates, except for occasional discharges through the papilla of Vater into the duodenum, is stored in the gall bladder. The storage of this amount of bile, which is many times the volume of the gall bladder, is possible because of the concentrating activity of the viscus. The bile is prevented from entering the duodenum continuously during secretion by the liver, by the regulatory mechanism at the distal

<sup>1</sup> Graham, Evarts A., Cole, W. H. and Copher, Glover H.: Visualization of the Gall Bladder by the Sodium Salt of Tetrabromphenolphthalein, Jour. Am. Med. Assn., 1924, **82**, 1777.

end of the common duct. As a result of almost complete closure of the common duct during fasting, the bile enters the gall bladder.

The filling of the gall bladder seems to depend almost entirely upon the occlusion of the common duct at its distal end. This fact has been adequately proven by cholecystography. If, after the injection of a halogenated phenolphthalein used for visualizing the gall bladder, the action of the sphincter of the common duct is obviated by the insertion of a properly fitting cannula into the intramural portion of the common duct, or if digestion is in progress, no shadow of the gall bladder will be obtained. Normally, after the injection of phenoltetraiodophthalein in a fasting subject, the bile enters the gall bladder and the iodine it contains casts a shadow on a film when exposed to the roentgen-ray.

#### THE REGULATION OF THE FLOW OF BILE INTO THE DUODENUM.

The regulatory mechanism at the duodenal end of the common bile-duct is of great importance. It regulates the discharge of the bile from the liver and the gall bladder into the intestine and is one of the necessary factors for the storage of bile in the gall bladder. This control has been considered by many clinicians and laboratory investigators to be exerted almost wholly by the so-called sphincter of Oddi. However, there is considerable uncertainty as to the influence of the sphincter of Oddi over the biliary flow. Even the existence of a distinct anatomical structure has been in doubt. A distinct sphincter cannot always be found apart from the fibers of the muscle coats of the duodenum. The interlacing of the muscle fibers around the duct with the muscle fibers of the duodenum is so intimate that it is difficult to conclude that there is an independent action of two groups of fibers. Nevertheless, it is the opinion of most investigators that such a distinct group of muscle fibers, the sphincter of Oddi, is present in most animals and in man, and would act as a sphincter.

The fact that bile normally passes into the duodenum intermittently rather than continuously is well known. Burget,<sup>1</sup> Carlson,<sup>2</sup>

<sup>1</sup> Burget, G. E.: The Regulation of the Flow of Bile: *Am. Jour. Physiol.*, 1925, **74**, 585; Regulation of Flow of Bile: II. Effect of Eliminating Sphincter of Oddi, *Am. Jour. Physiol.*, 1926, **79**, 130; The Regulation of the Flow of Bile: III. The Rôle of the Gall Bladder, *Am. Jour. Physiol.*, 1927, **81**, 422.

<sup>2</sup> Carlson, A. J.: Physiology of the Liver: Present Status of our Knowledge, *Jour. Am. Med. Assn.*, 1925, **85**, 1468.

Copher and Kodama<sup>1</sup> believe that the most important factor resisting the continuous outflow of bile from the common duct is the tonus of the duodenum, rather than the successive relaxation and contraction of the sphincter of Oddi. The regulation of the outflow is accomplished by the wall of the duodenum, due to the fact that the common bile-duct passes between the muscular coats of the intestine in an oblique manner. This anatomical arrangement of the muscle fibers of the intestinal wall about the intramural portion of the duct constitutes a sphincter-like mechanism which is dependent on the tonicity of the duodenum and makes it possible for peristalsis to be a factor in the emptying of the duct. (Fig. 54.)

It is interesting to find that Saunders,<sup>2</sup> in 1797, wrote the following: "The bile having arrived at the trunk of the hepatic duct, naturally passes forward into the duodenum. But we are not to consider its motion as uniformly progressive and without interruption; for it is probable, from the oblique manner in which the biliary duct perforates the substance of the intestine, that the peristaltic motion of that gut, consisting in part of the contraction of its circular and in part of that of its longitudinal fibers, will, by compressing the duct at its termination, occasion frequent, but momentary interruption."

The normal tonus is sufficient to prevent a continuous flow from the duct and is consequently a great factor in the filling of the gall bladder. No great tonicity of the duodenum is necessary to close the small lumen of the duct. When the intraductal pressure becomes high enough, it overcomes this resistance and flows intermittently into the lumen of the duodenum.

Copher and Kodama<sup>3</sup> were also able to show by measuring pressure in the common duct and simultaneously recording the tonus, movements and changes of volume in the duodenum, that peristalsis, as well as other changes of tonicity, is a factor in the outflow of bile from the duct. The discharge of bile into the duodenum occurs especially during a relaxation phase of a peristaltic movement. Furthermore, rhythmic or pendular movements of the duodenum produce an alternate rise and fall of pressure in the common duct.

<sup>1</sup> Copher, Glover H. and Kodama, Shuichi: The Regulation of the Flow of Bile and Pancreatic Juice into the Duodenum, *Arch. Int. Med.*, 1926, **38**, 647.

<sup>2</sup> Saunders, William: A Treatise on the Structure, Economy and Diseases of the Liver: Together with an Inquiry into the Properties and Component Parts of the Bile and Biliary Concretions, first American from second London edition, Boston, printed for W. Pelham, 1797.

<sup>3</sup> Copher, Glover H. and Kodama, Shuichi: The Regulation of the Flow of Bile and Pancreatic Juice into the Duodenum, *Arch. Int. Med.*, 1926, **38**, 647.



FIG. 54.—The upper tracing records tonus, movements and volume changes in segment of duodenum between ligatures; A, distance of tracing above base-line, representing the volume of fluid in the segment at the beginning of experiment; B, small wave, corresponding to a rhythmic contraction; C to D, large wave, representing a peristaltic movement; E, volume of fluid in segment of duodenum at end of experiment. Increase of volume over A should be noted. The lower tracing records pressure and volume changes in the common bile-duct; 1, small wave, representing change of pressure in duct corresponding to B, a rhythmic contraction; 2, at this point a pressure of 100 mm. of physiological sodium chloride solution in the duct was started. The fall in pressure is steplike, corresponding to a relaxation phase of a peristaltic movement. 3, a constant pressure of 100 mm. of physiological sodium chloride solution was resumed. The fall in pressure from 2 to 3 represents the passage of 1.75 cc. of physiological sodium chloride solution from the common duct into the duodenum. (Copher and Kodama, *Archives of Internal Medicine*.)



As these movements constrict the intra-mural portion of the duct, they may possibly aid by acting as a pumping mechanism in the expulsion of bile from the duodenal papilla. Potter and Mann<sup>1</sup> had previously recorded rhythmic waves of pressure in the common duct which they thought due to the mechanism of Oddi's sphincter. They were unable to determine any relationship between the pressure waves in the duct and peristalsis of the duodenum.

Evidence that the normal tonus and peristalsis of the duodenum is an important factor in the regulation of the flow of bile into its lumen, is substantiated by the experimental use of drugs. It was found by us that drugs that affect the tonus of the duodenal musculature affect, accordingly, the discharge of bile from the duct.

It may be concluded from the accumulated evidence that the function of the sphincter of Oddi has been over-emphasized and that the tonicity of the duodenal wall is one of the major factors in the regulation of the flow of bile into the duodenum. It is to be noted that the chief action of the mechanism is to furnish resistance to the outflow of bile from the common duct and so cause it to back up into the gall bladder. Adequate pressure in the common duct from the secretory pressure of the liver or contracting force of the gall bladder is capable of overcoming this resistance. When a high intraductal pressure has been attained, the sphincter still may partially regulate the *vis-a-tergo*.

The activity of the musculature of the lower portion of the common duct has been studied by many other investigators. Especial attention has been paid to it by those investigating Meltzer's law. This subject is discussed in the succeeding paragraphs, under reciprocal activity of the gall bladder and the common duct sphincter.

The sphincter of Oddi, when present, is doubtless a factor in the regulatory mechanism which has been described. Its relaxation and contraction are doubtless coördinated with the other factors involved in the regulation of the flow of bile. The muscle fibers in the wall of the common duct are probably capable of independent contraction. By this means the lumen of the duct may be occluded and the flow of bile stopped. The ability of the common duct wall to contract has been demonstrated by recording changes of pressures in the lumen. Naunyn found that when he stimulated electrically the mucous membrane of the common duct in live animals, the muscle fibers in the wall contracted most vigorously 1 cm. above.

<sup>1</sup> Potter, J. C. and Mann, F. C.: Pressure Changes in the Biliary Tract, *Am. Jour. Med. Sci.*, 1926, **171**, 202.



Burget and Brocklehurst,<sup>1</sup> and Mann and Higgins<sup>2</sup> have described a specialized type of bile-expelling mechanism in the guinea-pig in the form of an ampulla, found in the distal portion of the common bile-duct.

### CONCENTRATION OF BILE IN THE GALL BLADDER.

The bile during its stay in the gall bladder is concentrated by the loss of water and by the addition to it of mucin derived from the cells lining the bladder. The difference in the gross appearance of the bile in the gall bladder from that coming directly from the liver has long been known. Later, the concentrated character of the bile in the gall bladder was shown by the comparison of the chemical composition of human bile obtained from the gall bladder with that procured from a fistula of the common bile-duct after removal of the gall bladder. Analyses demonstrate that bile from the gall bladder contains many times more solids than bile which has not entered the gall bladder, and that for the most part these solids are normal constituents of the liver bile.

Conclusive evidence of the absorptive power of the gall bladder was demonstrated by Rous and McMaster,<sup>3</sup> who made a quantitative study of the ability of the gall bladder to concentrate the pigments of the bile. They collected the bile of dogs, which was secreted simultaneously, in two portions, one of which had passed into the gall bladder, while the other portion was not allowed to enter the gall bladder. Analyses showed that the amount of pigment per cubic centimeter in the bile from the gall bladder might be ten times as much as that in the bile which has not entered the bladder.

The rapidity of the development of jaundice has been shown by Mann and Bollman<sup>4</sup> to be influenced by the absorptive function of the gall bladder. If the common bile-duct is ligated and the gall bladder left intact, signs of jaundice, that is, bile pigment in the urine and plasma, and pigmented sclerotics, do not develop for from thirty-six to forty-eight hours after the ligation. If the gall bladder is removed at the time of the ligation of the common duct,

<sup>1</sup> Burget, G. E. and Brocklehurst, R. J.: An Undescribed Bile-expelling Mechanism in the Guinea-pig, *Proc. Soc. Exper. Biol. and Med.*, 1927, **24**, 843.

<sup>2</sup> Mann, F. C. and Higgins, G. M.: Emptying of Gall Bladder and Mechanism of Common Bile Duct of Guinea-pig, *Proc. Soc. Exper. Biol. and Med.*, 1927, **24**, 931.

<sup>3</sup> Rous, P. and McMaster, P. D.: The Concentrating Activity of the Gall Bladder, *Jour. Exper. Med.*, 1921, **34**, 47.

<sup>4</sup> Mann, F. C. and Bollman, J. L.: The Relation of the Gall Bladder to the Development of Jaundice Following Obstruction of the Common Bile Duct, *Jour. Lab. and Clin. Med.*, 1925, **10**, 540.

bile pigment appears in definite amounts in the urine and plasma within three to six hours after operation. This difference in the rate of accumulation of bile pigment is taken as evidence of the ability to concentrate the bile secreted by the liver.

This absorptive power of the gall bladder is of fundamental importance in visualizing the normal gall bladder by the roentgen-ray after the administration of suitable substances which are excreted in the bile by the liver and concentrated in the gall bladder. This concentrating ability is one of the factors involved in the production of a shadow of the gall bladder at different intervals after administration of the iodized phenolphthaleins. Chemical analyses made during the early experimental work on cholecystography showed that the average concentration of the halogen per unit volume of bile in the gall bladders which cast shadows of maximum density, was several times that of the bile which was not allowed to enter the gall bladder.<sup>1</sup> The analyses also revealed that there is a fairly constant rate of excretion of the halogen in the bile and that the output of the halogen is independent of the rate of excretion of the bile.

A study of the concentration by the gall bladder of cholecystographic mediums and of bilirubin has been made by Bollman, Caylor and Kirklin.<sup>2</sup> They found that the bilirubin content of the gall bladder did not parallel the density of the cholecystographic shadow.

Most of the experimental data on the concentration of bile in the gall bladder relates to the absorption of water. However, other substances are known to be readily absorbed. Harer, Hargis, and van Meter<sup>3</sup> demonstrated the absorptive action of the gall bladder by injecting into it potassium-sulpho-cyanide and by finding the injected chemical in the lymph vessels shortly afterward by testing with ferric chloride. Boyd<sup>4</sup> used the Prussian blue reaction to study the absorptive activity of the gall bladder. Mentzer<sup>5</sup> found that the mucosa of the gall bladder can absorb lipoids. It is possible that cholesterol, fat and a few other substances are

<sup>1</sup> Copher, Glover H.: Cholecystography: Appearance and Disappearance of the Shadow, *Jour. Am. Med. Assn.*, 1925, **84**, 1563.

<sup>2</sup> Bollman, J. L., Caylor, H. D., Kirklin, B. R.: The Concentration of Cholecystographic Mediums and of Bilirubin by the Gall Bladder, *Proceedings of the Staff Meeting of the Mayo Clinic*, 1927, **2**, 69.

<sup>3</sup> Harer, W. B., Hargis, E. H., and Van Meter, V. C.: Function of the Gall Bladder, *Surg., Gynec. and Obst.*, 1922, **34**, 307.

<sup>4</sup> Boyd, W.: Studies in Gall Bladder Pathology, *British Jour. Surg.*, 1922-1923, **10**, 337.

<sup>5</sup> Mentzer, S. H.: Cholesterosis of the Gall Bladder, *Am. Jour. Pathol.*, 1925, **1**, 383.

normally absorbed. Some investigators, however, have been of the opinion that bile enters by way of the cystic duct, but leaves only by resorption of all of its constituents through the walls of the bladder. This problem will be discussed in another paragraph.

The concentration of the content of the gall bladder is accomplished by the withdrawal of fluid by osmosis and diffusion. This process is nearly continuous because the human gall bladder, although collapsed at intervals, is probably never entirely empty. Specimens of bile which were obtained during various stages of emptying of the gall bladder as determined by cholecystograms, are dark and viscid, indicating that absorption of its contents progresses as the gall bladder empties.

The mucosa, the bloodvessels and the lymphatics are actively concerned with the process of concentration by the gall bladder. The muscularis of the wall keeps the walls of the bladder in contact with the content as the intravesical pressure fluctuates. A clinical and experimental study of these factors of concentration has been made by Spurling and Whitaker.<sup>1</sup>

An interesting study of the mucosa of the gall bladder and "the organ of absorption" has been made by Boyden.<sup>2</sup> He found in the gall bladder of a cat that the rugæ or mucosal folds bounding polygonal spaces, and giving the interior a honeycomb appearance, vary remarkably in changing from distention to collapse. These folds were not obliterated when the gall bladder was subjected to great internal pressure. When the gall bladder is collapsed, its lumen is nearly filled with fungiform projections of the mucosa. It is probable these observations hold true for the human gall bladder, since the mucosal arrangement of the human gall bladder is very similar to that of the cat. Boyden concluded from his study that the most rapid absorption probably takes place in a partially collapsed gall bladder. During partial collapse the surface of the mucosa in apposition to the bile is more vascular than it is during distension.

The lymphatics, capillaries and venules are active in the function of absorption by the gall bladder. The relative importance of each has not been finally determined. Copher and Kodama<sup>3</sup> studied the influence of the vascular and lymphatic systems in the

<sup>1</sup> Spurling, Roy G. and Whitaker, L. R.: End-results of Cholecystostomy as Shown by the Cholecystogram, *Surg., Gynec. and Obst.*, 1927, **64**, 463.

<sup>2</sup> Boyden, E. A.: The Effect of Natural Food on the Distension of the Gall Bladder with a Note on the Change in Pattern of the Mucosa as it Passes from Distension to Collapse, *Anat. Rec.*, 1925, **30**, 333.

<sup>3</sup> Copher, Glover H. and Kodama, S.: Unpublished work.

production of a cholecystogram. It was believed that one of the factors determining the density of the shadow of a cholecystogram is the ability of the gall bladder to concentrate its content. Ligation of the cystic artery and vein of a dog lessened the density of a shadow considerably. The blood supply to the gall bladder from its bed in the liver is adequate to prevent gangrene. There were no shadows procured when the gall bladder was removed from its bed with the cystic vessels intact. This experiment was of little value because of the necessary trauma. Destruction of the superficial lymphatics of the gall bladder and cystic duct, which are easily seen, by a pin-pointed actual cautery, fixative agents, etc., either prevented the appearance of a shadow or allowed the production of one with less density than normal, and of less density than after ligation of cystic bloodvessels. Though these experiments are not conclusive, they are significant in that they indicate the lymphatics and blood supply are both necessary for the production of a normal cholecystogram.

The extra-hepatic ducts probably do not normally possess a concentrating activity. Rous and McMaster<sup>1</sup> are of the opinion that the bile-ducts not only do not concentrate their content but may dilute the bile with a thin secretion of their own.

### THE CYSTIC DUCT AND THE VALVES OF HEISTER.

The considerable anatomical variations of the cystic duct and its valves have been described in another chapter. The importance of their physiological functions naturally must vary with the individual types. In most instances the duct is flexed on itself in a curve, in some instances it is S-shaped and occasionally it is straight. Likewise, the folds of mucus membrane in the duct, the valves of Heister, vary a great deal in form and number. In a few human specimens they are absent.

One of the obvious functions of the cystic duct would seem to be for it to serve as a passageway for the flow of bile to and from the gall bladder. While no one seems to have doubted that the bile normally enters the gall bladder by way of the cystic duct, there are some investigators who have questioned if the gall bladder normally empties itself through this channel. Sweet<sup>2</sup> stated, "The position of the gall bladder, the provision of two valvular

<sup>1</sup> Rous, P. and McMaster, P. D.: The Concentrating Activity of the Gall Bladder, *Jour. Exper. Med.*, 1921, **34**, 47.

<sup>2</sup> Sweet, J. E.: The Gall Bladder: Its Past, Present and Future, *Int. Clin.*, 1924, **1**, 187.



structures at its outlet, which are mechanically designed to permit inflow and hinder outflow, lead me to the conclusion that under normal conditions whatever passes into the gall bladder through the cystic duct never passes out again through the cystic duct." Halpert<sup>1</sup> and Demel and Brummelkamp<sup>2</sup> are of the same opinion and also stress the mechanical hindrance to the outflow of bile. Sweet and Halpert believe that bile leaves the gall bladder by absorption.

However, studies of the gall bladder made by using materials opaque to the roentgen-ray show that these substances leave the gall bladder by way of the cystic duct and that it is probable most of the bile normally leaves it in the same manner. These methods simulate the normal process and permit visualization of it while it is in progress. For these reasons the results by cholecystography are as equally convincing as those of Auster and Crohn,<sup>3</sup> Diamond,<sup>4</sup> Winkelstein<sup>5</sup> and Mentzer,<sup>6</sup> who observed that following the injection of dyes into the gall bladder, they could be found in the intestine.

Copher<sup>7</sup> found by employing cholecystography that by far the greater portion of iodine leaves the gall bladder, as it entered, by way of the cystic duct. Dense shadows of the gall bladder were obtained in dogs by the intravenous injection of sodium tetraiodophenolphthalein. The common bile-duct was then occluded by two ligatures and cut between them. The common duct was ligated rather than the cystic duct, because ligation of the cystic duct necessarily would occlude some of the blood and lymphatic supply. The shadows of the gall bladders persisted until death of the animals or the reestablishment of an opening of the common duct. One dog lived eleven days after such a procedure. The final roentgen-ray shadows of the gall bladders were nearly as dense as the first ones made. These experiments indicate that most of the iodine in the bile producing a shadow normally leaves the gall

<sup>1</sup> Halpert, B.: *Neue Wege in der Gallenblasenforschung: I. Orthologie der extrahepatischen Gallenwege; II. Zur Orthologie und Pathologie die Gallenwege*, Med. Klin., 1830-1924, **20**, 406.

<sup>2</sup> Demel, R. and Brummelkamp, R.: *Ein Beitrag zur Funktion der Gallenblase; Ein tierexperimentelle Studie*, Mitt. Grenzgeb. Med. A. Chir., 1923-1924, **37**, 515.

<sup>3</sup> Auster, L. S. and Crohn, B. B.: *Notes on Studies in the Physiology of the Gall Bladder*, Am. Jour. Med. Sci., 1922, **164**, 345.

<sup>4</sup> Diamond, J. S.: *Experimental Study of Meltzer-Lyon Test, with Comment on Physiology of Gall Bladder and Sphincter Vateri*, Am. Jour. Med. Sci., 1923, **166**, 894.

<sup>5</sup> Winkelstein, A.: *The Motor Mechanism of the Gall Bladder*, Jour. Am. Med. Assn., 1923, **80**, 1748.

<sup>6</sup> Mentzer, S. H.: *Cholesterosis of the Gall Bladder*, Am. Jour. Pathol., 1925, **1**, 383.

<sup>7</sup> Copher, Glover H.: *Cholecystography: Appearance and Disappearance of the Shadow*, Jour. Am. Med. Assn., 1925, **84**, 1563.



bladder through the cystic duct rather than by absorption through the walls of the vesicle.

A small portion of the iodine or of other halogens may normally pass through the wall of the gall bladder during its concentrating activity. Phenoltetrahalogenphthalein may be demonstrated in the lymphatics emerging from the gall bladder after ligation of the common duct and intravenous injection of the dyes. Likewise, bile salts and pigments have been found in the lymph collected from the lymphatics of the gall bladder by canalization. Other salts that are not normally found in bile may be introduced into the gall bladder and later collected from the lymphatics draining the organ.

The investigation of whether or not the contents of the gall bladder may leave it by way of the cystic duct was carried out with the roentgen-ray in a different manner by Abramson.<sup>1</sup> He injected into the gall bladder of a dog a solution of silver and saw by fluoroscopy that globules of the opaque solution passed through the bile ducts into the duodenum.

A more extended study of the mechanism of the gall bladder by use of the roentgen-ray has been made by Whitaker,<sup>2</sup> by injecting iodized oil into the gall bladder of dogs. Five minutes after feeding egg-yolk to a dog, he found the cystic and common duct filled with the oil, which soon passed into the duodenum.

These experiments by the different investigators can only be interpreted as showing that the gall bladder, except for those constituents of the bile which are absorbed, empties itself through the cystic duct.

It is probable that the cystic duct may have some valvular action. Jacobson and Gydeson<sup>3</sup> believe that the curvature of the cystic duct is a factor in emptying the gall bladder. They found that the intact gall bladder of animals can be distended by great pressure without forcing bile out of the cystic duct, though it can be readily emptied by longitudinal traction on the duct. The increased pressure served to enhance the valvular action of the kink in the duct and prevent exit of the content. Traction on the gall bladder tends to straighten the kink and allow egress of bile.

Copher<sup>4</sup> repeated the experiments of Jacobson and Gydeson in

<sup>1</sup> Abramson, H. A.: Visualization of the Gall Bladder of the Dog by the Roentgen-ray, *Proc. Soc. Exper. Biol. and Med.*, 1924, **21**, 407.

<sup>2</sup> Whitaker, L. R.: The Mechanism of the Gall Bladder, *Am. Jour. Physiol.*, 1926, **78**, 411.

<sup>3</sup> Jacobson, C. and Gydeson, C.: The Function of the Gall Bladder in Biliary Flow, *Arch. Surg.*, 1922, **5**, 374.

<sup>4</sup> Copher, Glover H.: Unpublished work.

dogs, and concluded also that the curvature of the duct and its valves may affect in some cases the rate of passage of bile into or out of the gall bladder. It is improbable that the valves are capable of completely obstructing the flow of bile in either direction in the duct. No one has demonstrated a true muscular sphincter in the wall of the cystic duct.

An anatomical and physiological study of the valves of Heister has been made by Mentzer.<sup>1</sup> He studied the patency of the cystic ducts of 22 normal gall bladders obtained at necropsy. His anatomical study of the valves did not favor either the idea that the valves aid in the storage of bile in the gall bladder, or that they prevent bile from leaving the fundus by way of the cystic duct. Mentzer concluded, after he found that solutions passed in either direction through the cystic duct with equal facility, though the valves are not very important, that they may check the rapid passage of bile into or out of the gall bladder. Mann<sup>2</sup> found the neck of the gall bladder to be capable of maintaining pressure from either side and suggested that the sphincteric control of the neck of the gall bladder may play a part in the retention of bile in the viscus for concentration.

Sweet<sup>3</sup> states, in discussing Mentzer's findings that he has never found a specimen from the human being which did not show valves of Heister, although they vary greatly in number and shape. He has not found them in any animal. Sweet's conclusions concerning the cystic duct of the human being are: "First, it is an extremely tortuous tube containing on the inside, throughout its entire length an arrangement of folds of mucous membrane which are placed in a more or less spiral fashion, but which divide the cystic duct essentially into a series of little chambers. The openings from one chamber into the next are not opposite each other but are so placed that the channel of flow is even more tortuous than would be determined by the external form alone; second, the actual number of these valves is inconstant and the shape of the chambers formed by them is never the same in any two specimens; third, the purpose of this curious arrangement is not clear. It might be a mixing device, it might be a device to impede the flow of bile from the gall bladder."

In whatever manner the cystic duct and its valves may affect the rate of flow of bile through its lumen, it is probable that its mucous membrane has an absorptive activity similar to that of the gall bladder.

<sup>1</sup> Mentzer, S. H.: The Valves of Heister, *Arch. Surg.*, 1926, **13**, 511.

<sup>2</sup> Mann, F. C.: The Functions of the Gall Bladder, *Physiol. Rev.*, 1924, **4**, 251.

<sup>3</sup> Sweet, J. E.: The Importance to Surgery of the Cystic Duct, *Am. Jour. Surg.*, 1927, New Series, **3**, 274.

**MECHANISM OF THE EMPTYING OF THE GALL BLADDER.**

One of the major problems concerning the gall bladder has been regarding the mechanism involved in its emptying. It is believed by some workers that the gall bladder is capable of emptying itself somewhat in the same manner as the urinary bladder, while others consider it largely a passive organ subject to changes of tonus and to the varying pressures in the hepatic and common ducts. Recent investigations by us made by visualizing the gall bladder suggest that the emptying of the viscus is a complicated process involving a combination of these factors.

As has been stated, early in the experimental work on cholecystography it was found that the stomach and duodenum should not contain food in order to secure a good cholecystogram after administration of a halogenated phenolphthalein. If gastric digestion is in progress, bile is permitted to enter the duodenum too freely by the common duct sphincter, and the bile containing iodine will not enter the gall bladder to produce a shadow. Likewise it was observed that if food was taken after a cholecystogram had been obtained in animals or man, there was a rapid reduction of the size of the shadow which indicated an outpouring of bile from the gall bladder. There was such a marked reduction and rapid disappearance of the shadow, in some instances, after the ingestion of food as to leave little doubt that the gall bladder was emptying in response to digestive processes.<sup>1</sup>

Copher, Kodama and Graham<sup>2</sup> made an extensive study of this emptying process. Attempts were made to observe contraction waves in the gall bladder such as occur in other parts of the alimentary tract, by using the fluoroscope. None were observed. Likewise, stimulations by trauma, electricity and chemicals did not produce contraction of the gall bladder in animals. Rhythmic contractions were obtained on a kymograph in an unanesthetized dog by placing a small rubber bag in his gall bladder. They could

<sup>1</sup> As a matter of history it may be of interest to state that fortunately at the beginning of the work on cholecystography the first dog which was injected showed a good shadow of its gall bladder. Six dogs in succession, which were then injected, all failed to have their gall bladders visualized. At first we were at a loss to explain the failures, but later it occurred to us that it might be necessary for the stomach and duodenum to be empty. If it had not been for our initial success, we probably would have given up the whole idea as a fruitless one because of the successive failures.

<sup>2</sup> Copher, Glover H., Kodama, S. and Graham, Evarts A.: The Filling and Emptying of the Gall Bladder, *Jour. Exper. Med.*, 1926, **44**, 65.

not be accepted as true contractions, however, because somewhat similar movements occurred synchronously in a similar rubber bag placed in the upper abdomen away from the gall bladder. It was found, too, that if a daily dose of tetraiodophenolphthalein is given to a dog eating a mixed ration, the gall bladder shadow is always present. Though the shadow varied somewhat in form and size, the organ was apparently never entirely empty. This latter finding corresponds to the common knowledge among surgeons, that the gall bladder is never empty on exposure by laparotomy. This experimental evidence led to the conclusion that the emptying of the gall bladder is not accomplished by movements of its walls alone.

### FACTORS OF DILUTION AND INTERCHANGE OF BILE.

Factors of dilution and interchange of bile were found by Copher, Kodama and Graham<sup>1</sup> to be of great importance in the appearance and disappearance of the shadow of the gall bladder. The dilution and interchange is accomplished by the entrance of bile from the hepatic ducts into the gall bladder, which results in a gradual washing out of the contents of the gall bladder. This was proven by the following experiment: When all the hepatic ducts of a dog were ligated, leaving the cystic and common ducts intact, after a dense shadow of the gall bladder had been secured from tetraiodophenolphthalein, the shadow was found to persist for many days even though food was taken regularly. These experiments were repeated in a slightly different manner by ligating the hepatic ducts and filling the gall bladder with iodized oil. The dogs were then given meals of egg-yolks and cream. Boyden<sup>2</sup> showed that these foods are most efficient in emptying the gall bladder of cats. The shadows did not disappear in a few hours, as they normally do after a Boyden meal, but persisted for days. (See Figs. 55 to 58.)

Dilution expresses itself as a factor in the normal emptying of the gall bladder in the formation of a cholecystogram. Phenoltetraiodophthalein is excreted in the bile shortly after intravenous injection. The closure of the lower end of the common duct diverts a considerable portion of the bile into the gall bladder. The amount of bile secreted is probably not large, comparatively, since the animal

<sup>1</sup> Copher, Glover H., Kodama, S. and Graham, Evarts A.: The Filling and Emptying of the Gall Bladder, *Jour. Exper. Med.*, 1926, **46**, 65.

<sup>2</sup> Boyden, E. A.: The Gall Bladder in the Cat, *Anat. Rec.*, 1922-1923, **24**, 388.



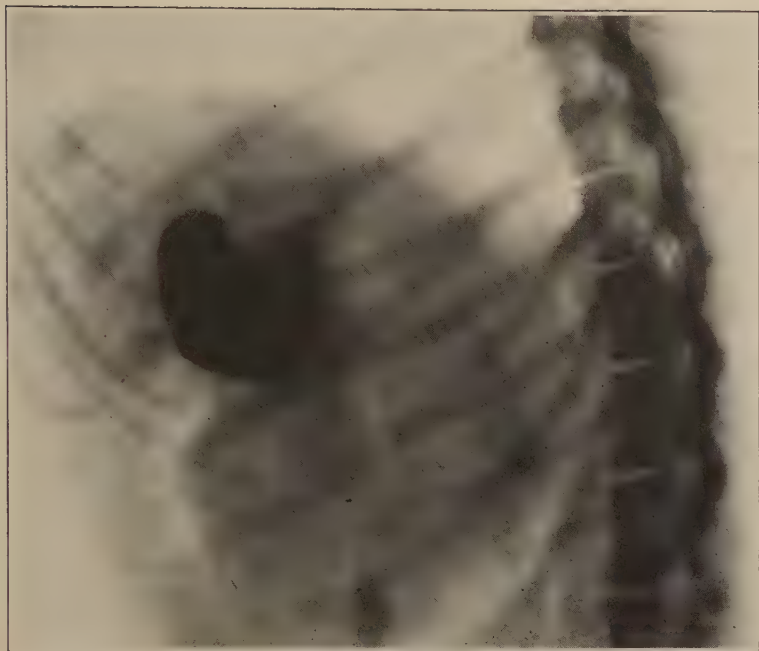


FIG. 55.—Gall bladder of dog containing lipiodol. To prevent the entrance of bile into the gall bladder, the hepatic ducts were ligated at the time of the introduction of the lipiodol. In this and all the following figures the x-rays were directed through the side of the animal which was standing on his four feet in the normal position.

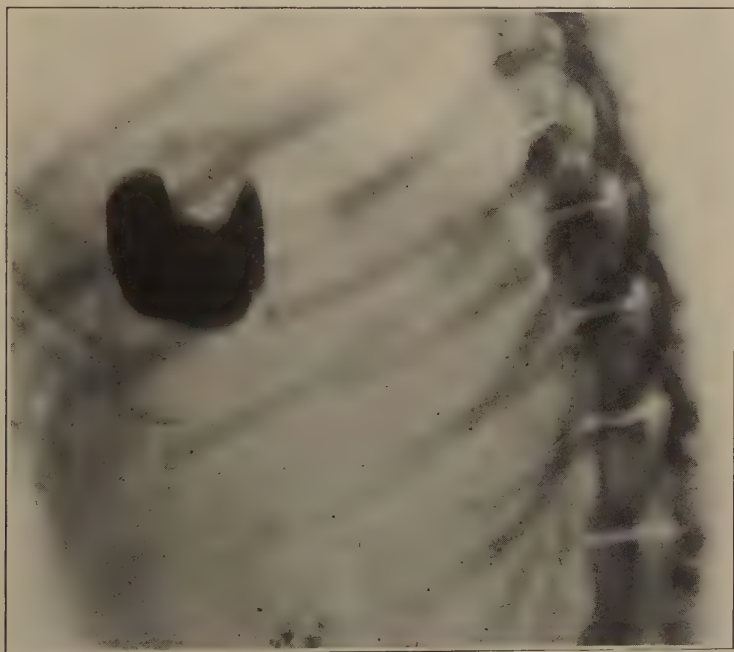


FIG. 56.—One hour and forty-five minutes after the administration of Boyden's meal of egg-yolk and cream and one hour and forty-five minutes after the picture shown in Fig. 55 was made. Some of the lipiodol has reached the intestine but the gall bladder has not diminished in size appreciably.



is fasting. The addition of iodine to the bile in the gall bladder proceeds. The gall bladder becomes distended. At this time we may obtain our first shadow of the gall bladder by exposure to the roentgen-ray. It is a large and faintly visible one. The amount of iodine in the vesicle increases by new additions of bile as the concentrating activity of the gall bladder proceeds simultaneously. The iodine content becomes great enough to cast the densest shadow in eight to fifteen hours after injection of the dye. The



FIG. 57.—Seven days after the administration of the fat meal. The gall bladder has diminished in size but has not emptied itself of the lipiodol because, as the hepatic ducts had been ligated, the bile could not wash out the gall bladder. During this period of seven days the dog had food and water constantly in his cage.

shadow at this time is quite dense, and is smaller than earlier in the cycle. The change in size of the shadow is partially due to the absorptive action of the wall of the gall bladder. At this period the iodine has probably been almost entirely excreted by the liver. Since iodine is no longer present in the bile coming from the liver, the shadow gradually disappears as dilution of the iodine in the gall bladder progresses, along with further emptying produced by what-

ever contractions are undergone by its wall. In the meantime, also, food has been given to the patient and the disappearance of the shadow is hastened by an increased secretion of bile and a relaxed common duct sphincter. The backing up of unconcentrated bile from the liver mechanically aids in the expulsion of the concentrated bile in the gall bladder.

Further proof that the interchange of bile in a "washing out"

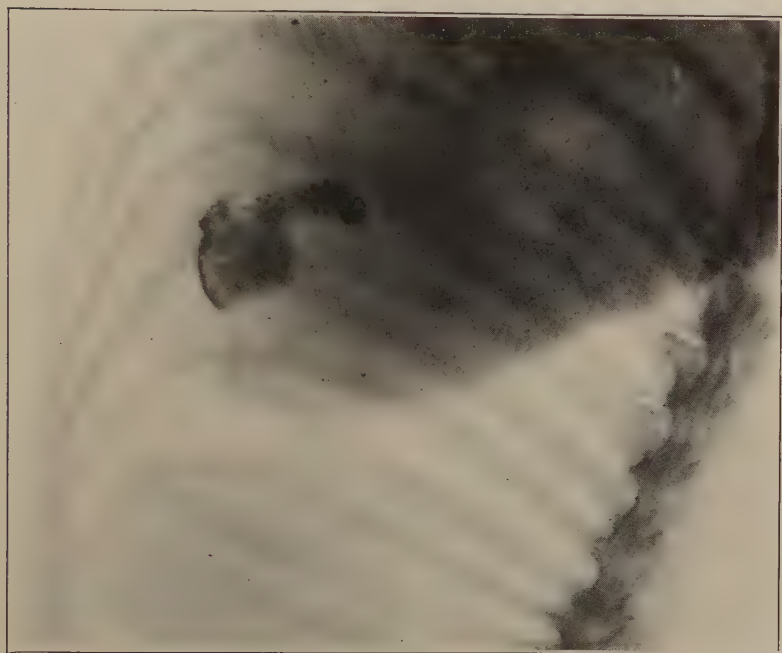


FIG. 58.—Thirty days after the administration of the fat meal. The shadow appears larger and presents globules, because the ligatures had cut partly through the hepatic ducts, permitting some bile to enter the gall bladder and to emulsify the oil in the lipiodol. But not enough hepatic bile was entering the gall bladder to wash out the lipiodol. If intrinsic contractions alone can empty the gall bladder, then it certainly should have emptied itself during one month's time. This strongly indicates that the washing out of the gall bladder by the ingress of fresh bile from the liver is an essential part of the mechanism.

manner is a considerable factor in the normal emptying is offered by the results obtained by placing an artificial gall bladder in several dogs. A thin rubber bag the size of a gall bladder was placed in a cystic duct of a dog by means of a short glass cannula after cholecystectomy. The animal was given a dose of tetraiodophenolphthalein after the surgical operation. The cycle of shadows

produced by the artificial rubber gall bladder was quite like that obtained from the normal gall bladder of the human, except that the shadows were not so dense and that they persisted over a longer period of time. The absence of the normal density can of course be explained by the failure of the rubber gall bladder to concentrate its contents.



FIG. 59.—Artificial gall bladder produced by uniting a small rubber bag to the cystic duct of a dog by means of a glass cannula after the normal gall bladder had been removed. A celloidin cylinder was then placed around the gall bladder to protect it from changes of intra-abdominal pressure. Twenty-four hours after an intravenous injection of tetraiodophenolphthalein the gall bladder is just faintly visible.

The experiment was repeated with the artificial gall bladder encased in a cylinder to prevent pressure from contiguous organs. The cylinder was not opaque to the roentgen-ray. The artificial gall bladder was found to fill and empty as in the preceding experiments. (See Figs. 59 to 62.)

As a result of these experiments and other observations, it seems justifiable to conclude that the factor of interchange of bile is a considerable one in the emptying of the gall bladder. This factor



FIG. 60.—At the end of forty-eight hours it is plainly visible.



FIG. 61.—At the end of ninety-six hours it is less plainly visible than before.

is intimately associated with the ability of the gall bladder to distend and then recoil, and with the periodic action of the sphincter of the common duct. This conclusion seems to be borne out further by Boyden's<sup>1</sup> observation that the filling and contraction of the gall bladder is of an intermittent nature and is closely associated with the periodic action of the sphincter papillæ.



FIG. 62.—At the end of one hundred and twenty hours the shadow of the gall bladder has practically disappeared. This experiment shows plainly that it is possible for the gall bladder to fill and empty itself without the aid of either changes in intra-abdominal pressure or muscular contraction. In this experiment the process of emptying was probably almost entirely due to the washing out of the gall bladder by a gradual inflow and outflow of bile from the liver. If the factor of changes of intra-abdominal pressure had been present the gall bladder would probably have emptied sooner. For further discussion of this experiment, see the text.

#### FACTOR OF ELASTIC RECOIL.

It is probable that the elasticity of the wall of the gall bladder is a factor in its emptying and aids in the interchange of hepatic bile with the content of the gall bladder. This passive mechanism is

<sup>1</sup> Boyden, E. A.: A Study of the Behavior of the Human Gall Bladder in Response to the Injection of Food; Together with Some Observations on the Mechanism of the Expulsion of Bile in Experimental Animals, *Anat. Rec.*, 1925, **33**, 201.



independent of an active contractile one and is dependent upon the relatively large amount of elastic tissue in the fibro-muscular coat. This layer not only probably helps in the emptying of the organ, but prevents its over-distention. The distensible walls equalize extremes of pressure within its lumen due to the variations of the rate of secretion of bile, to the variable state of contraction of the common duct sphincter, and to changes of intra-abdominal pressure.

The gall bladder can be easily distended and it has an elastic recoil when the inside pressure is suddenly relieved. This mechanical principle may function in the case of the distended gall bladder whose pressure is relieved slowly by relaxation of the ampullar end of the common duct. Boyden<sup>1</sup> observed that the response of the gall bladder to food is greatest when it is distended. He assumed that when the gall bladder contracted during distention, the action of the abundant elastic tissue in the wall increased the effectiveness of the smooth muscle. Burget,<sup>2</sup> also, believes the elasticity of the distended wall of the gall bladder passively aids in the flow of bile. Whitaker<sup>3</sup> found that the large shadows of gall bladders in fasting animals shrank in size after the sphincter of the common duct had been cut. A model of the gall bladder has been made by Kodama<sup>4</sup> which demonstrates the mechanical principle of elastic contraction.

### MOVEMENTS OF THE GALL BLADDER.

It has been noted that the shadow of the gall bladder varies in size, denoting that factors other than dilution or interchange of bile play a part in its emptying. The most important of these factors is the action of the wall of the gall bladder. The influence of the wall is exerted by its muscle fibers and elastic tissue. These constituents of the wall are of great functional significance.

The muscular coat of the gall bladder is composed of smooth muscle and interlacing bands of connective tissue. The muscle fibers interlace in all directions and according to Hendrickson,<sup>5</sup> the greatest number tend toward a transverse direction. The muscle tissue,

<sup>1</sup> Boyden, E. A.: A Study of the Behavior of the Human Gall Bladder in Response to the Injection of Food; Together with Some Observations on the Mechanism of the Expulsion of Bile in Experimental Animals, *Anat. Rec.*, 1925, **33**, 201.

<sup>2</sup> Burget, G. E.: The Regulation of the Flow of Bile: III. The Rôle of the Gall Bladder, *Am. Jour. Physiol.*, 1927, **81**, 422.

<sup>3</sup> Whitaker, L. R.: The Mechanism of the Gall Bladder and its Relation to Cholelithiasis, *Jour. Am. Med. Assn.*, 1927, **88**, 1542.

<sup>4</sup> Kodama, S.: A Model to Simulate the Mechanism of Emptying of the Gall Bladder, *Am. Jour. Physiol.*, 1926, **77**, 385.

<sup>5</sup> Hendrickson, W. F.: A Study of the Musculature of the Entire Extra-hepatic Biliary System, Including that of the Duodenal Portion of the Common Bile Duct and of the Sphincter, *Johns Hopkins Hosp. Bull.*, 1899, **9**, 221.

however, is practically limited to the region immediately beneath the mucosa, giving the impression, as Halpert has suggested, that it is really only a *muscularis mucosæ*, the chief function of which is to throw the mucous membrane into folds. The subserous layer is composed of densely interwoven elastic tissue bands. Boyden<sup>1</sup> has found the gall bladder to contain relatively much less muscle and relatively much more elastic tissue than the intestine. The fibro-muscular and subserous layers lend themselves nicely to the movements of the gall bladder. These movements are an active contraction and a passive reaction to the varying pressures in the hepatic and common ducts.

### CONTRACTIONS OF THE GALL BLADDER.

There is convincing evidence that the gall bladder has a contractile mechanism which exerts pressure on its contents. Doyon<sup>2</sup> first recorded graphically, slow, irregular but spontaneous contractions of the gall bladder by introducing a balloon filled with water into the fundus and connecting it with a recorder. Likewise, Bainbridge and Dale,<sup>3</sup> Okada,<sup>4</sup> Macht,<sup>5</sup> Mann and Giordano,<sup>6</sup> Taylor and Wilson<sup>7</sup> recorded rhythmic changes of pressure in the gall bladder which they believed were due to contractions of the wall. Burget<sup>8</sup> has recorded rhythmical tonus changes in the gall bladder, but he believes that "the gall bladder is incapable of contractions that might be construed as being of major importance in the flow of bile."

Much of the preceding experimental work on the physiology of the gall bladder and the extra-hepatic ducts was performed on anesthetized animals and the conclusions are therefore not entirely satisfactory. Potter and Mann,<sup>9</sup> however, devised a method of studying

<sup>1</sup> Boyden, E. A.: The Effect of Natural Food on the Distension of the Gall Bladder, with a Note on the Change in Pattern of the Mucosa as it Passes from Distension to Collapse, *Anat. Rec.*, 1925, **30**, 333.

<sup>2</sup> Doyon, M.: Mouvements spontanés des voies biliaires, *Arch. de Physiol. norm. et path.*, 1893, **5**, 710.

<sup>3</sup> Bainbridge, F. A. and Dale, H. H.: The Contractile Mechanism of the Gall Bladder and its Extrinsic Nervous Control, *Jour. Physiol.*, 1905, **33**, 138.

<sup>4</sup> Okada, S.: On the Contractile Movement of the Gall Bladder, *Jour. Physiol.*, 1915-1916, **50**, 42.

<sup>5</sup> Macht, D. I.: On the Comparative Effects of the Opium Alkaloids Individually and in Combination with Each Other on the Gall Bladder, *Jour. Pharmacol. and Exper. Therap.*, 1917, **9**, 473.

<sup>6</sup> Mann, F. C. and Giordano, A. S.: The Bile Factor in Pancreatitis, *Arch. Surg.*, 1923, **6**, 1.

<sup>7</sup> Taylor, N. B. and Wilson, M. J.: Observations upon the Contractions of the Gall Bladder, *Am. Jour. Physiol.*, 1925, **7**, 173.

<sup>8</sup> Burget, G. E.: The Regulation of the Flow of Bile. III. The Rôle of the Gall Bladder, *Am. Jour. Physiol.*, 1927, **81**, 422.

<sup>9</sup> Potter, J. C. and Mann, F. C.: Pressure Changes in the Biliary Tract, *Am. Jour. Med. Sci.*, 1926, **171**, 202.

simultaneously pressure in the gall bladder and the common ducts of unanesthetized animals by allowing to heal in position, before readings were made, a tube to the gall bladder and a "T" tube in the common duct near the duodenum. They found the average pressure in the gall bladder to be greater than that in the common duct. Besides finding rhythmic waves of pressure changes in the gall bladder, they found rhythmic waves of pressure in the common duct. The pressure in the gall bladder was found to rise as that in the duct fell, after which the waves approached each other and met. Repetitions of this phenomenon continued. Potter and Mann suggested that it was possible there are two types of pressure waves in the gall bladder, "one caused by a squashing action and another by a contraction of a peristaltic nature."

A study of the expulsion of the bile by the gall bladder, in unanesthetized dogs, has also been made by McMaster and Elman.<sup>1</sup> They measured the various pressures by permanently intubating the hepatic ducts, the gall bladder and the common duct. It was found that the taking of food caused the gall bladder forcibly to expel by recurring contractions "some portion of its content." At the same time that the gall bladder contracted, the resistance to the flow of bile into the gut markedly lessened. The pressure developed within the gall bladder was sufficient to force bile through the ampulla of Vater under such conditions. The contractions studied in these experiments were slow and often had a duration of several minutes, although only a little bile was ejected at any one time.

It was observed by Boyden,<sup>2</sup> in 1923, that the gall bladder in cats is found almost completely collapsed a few hours after a meal of egg-yolk and cream. He found a functional periodicity of the gall bladder in relation to meals, of three main phases: A period of slow emptying, a collapsed period, and a period of slow filling.

Diminution in the size of the gall bladder in the human was observed by Sachs,<sup>3</sup> Pribram<sup>4</sup> and Matsuo,<sup>5</sup> following duodenal lavage with magnesium sulphate after the method of Lyon. Contractions of the gall bladder in fishes, guinea-pigs and dogs, in response to a diet rich in fat, were seen by Higgins and Mann.<sup>6</sup>

<sup>1</sup> McMaster, P. D. and Elman, R.: On the Expulsion of Bile by the Gall Bladder, and a Reciprocal Relationship with the Sphincter Activity, *Jour. Exper. Med.*, 1926, **44**, 173.

<sup>2</sup> Boyden, E. A.: The Gall Bladder in the Cat, *Anat. Rec.*, 1922-1923, **24**, 388.

<sup>3</sup> Sachs, Adolph: Lyon-Meltzer Gall Bladder Drainage, *Nebraska Med. Jour.*, 1921, **6**, 225.

<sup>4</sup> Pribram, E. E.: Peptone Gall Bladder Reflex, *Klin. Wchnschr.*, 1923, **2**, 1590.

<sup>5</sup> Matsuo, I.: Magnesium Sulphate as a Cause of the Evacuation of the Gall Bladder, *Jour. Am. Med. Assn.*, 1924, **83**, 1289.

<sup>6</sup> Higgins, G. M. and Mann, F. C.: Observations on the Emptying of the Gall Bladder, *Am. Jour. Physiol.*, 1926, **78**, 339.

The results of the experiments obtained by visualizing the gall bladder with the roentgen-ray indicate, equally as well as measurements of pressure, that the intrinsic musculature of the viscus may contract. However, Winkelstein<sup>1</sup> sutured four small silver discs on the serous surface of the gall bladder of the dog and was unable to observe, with the roentgen-ray, any change in size before or after feeding. Likewise, Abramson<sup>2</sup> was unable to see the gall bladder filled with neosilvol empty under the fluoroscope. Nevertheless, he once saw an opaque solution of sodium iodide spurt from the gall bladder. Potter and Mann,<sup>3</sup> with the fluoroscope observed the gall bladder of a dog filled with a barium solution. The vesicle was seen to undergo a movement, and opaque material was projected at intervals from the neck. Kaznelson and Reiman<sup>4</sup> demonstrated by cholecystography changes of size of the human gall bladder, after introduction of oil into the duodenum and after injection of pituitrin, which they interpret as being due to a contraction of the gall bladder wall.

The mechanism involved in the expulsion of bile from the gall bladder has been studied by Boyden<sup>5</sup> and by Whitaker.<sup>6</sup> The response of the gall bladder, after ingestion of egg-yolk, was studied in experimental animals by a technique devised by Whitaker. This consists of emptying the gall bladder of its bile through the fundus at laparotomy and replacing the bile with an iodized oil. The iodized oils give a sharper contrast in films to the roentgen-ray than the dyes used in cholecystography. Boyden and Whitaker found changes in the shadows of the cat's gall bladder after ingestion of yolk, which they interpreted as due to active muscular contraction. They demonstrated the expulsion of the iodized oil by the gall bladder through the cystic and common ducts into the duodenum.

In an elaborate study of a series of 10 cholecystograms, Boyden,<sup>7</sup> computed the varying volumes of bile in the gall bladder of the

<sup>1</sup> Winkelstein, A.: The Motor Mechanism of the Gall Bladder, *Jour. Am. Med. Assn.*, 1923, **80**, 1748.

<sup>2</sup> Abramson, H. A.: Visualization of the Gall Bladder of the Dog by the Roentgen-ray, *Proc. Soc. Biol. and Med.*, 1924, **21**, 407.

<sup>3</sup> Potter, J. C. and Mann, F. C.: Pressure Changes in the Biliary Tract, *Am. Jour. Med. Sci.*, 1926, **171**, 202.

<sup>4</sup> Kaznelson, P. and Reiman, F.: Erfahrungen ueber die roentgenologische Darstellung der Gallenblase mittels Tetrabromphenolphthalein nach Graham-Cole, *Klin. Wehnschr.*, 1925, **4**, 1390.

<sup>5</sup> Boyden, E. A.: The Effect of Natural Food on the Distension of the Gall Bladder, with a Note on the Change in Pattern of the Mucosa as it Passes from Distension to Collapse, *Anat. Rec.*, 1925, **30**, 333.

<sup>6</sup> Whitaker, L. R.: The Mechanism of the Gall Bladder, *Am. Jour. Physiol.*, 1926, **78**, 411.

<sup>7</sup> Boyden, E. A.: *Loc. cit.*



human following the ingestion of food, and constructed a contraction curve. He found from this study that the changes in shape of the gall bladder after meals indicate that most of the bile stored in the organ is expelled slowly by its musculature during the first part of a meal. The contraction was found to be of an intermittent nature, the first phase being the most effective. Filling of the gall bladder was also intermittent and was correlated with periodic action of the sphincter of the common duct. The latter experiments by Boyden would seem to confirm the ideas previously expressed by Copher, Kodama and Graham<sup>1</sup> on the mechanism of the emptying of the gall bladder.

The emptying of the gall bladder has been studied by Hamrick,<sup>2</sup> using iodized oil and the roentgen-ray to observe its movements. He believes the gall bladder empties a portion of its content into the duodenum with digestion as a result of periodic contractions of its musculature.

From all of this discussion it would seem that there is at hand sufficient evidence to justify the belief that the gall bladder may undergo intrinsic contractions of its musculature. But after all, the important question is, are these contractions effective in emptying the organ? It is the belief of many that they are, and some even hold the opinion that the only mechanism of emptying is by these intrinsic contractions. This seems to be the opinion of Whitaker, Boyden, Higgins and Mann, McMaster and Elman, etc. The proof for this opinion, however, is still lacking. Higgins and Mann could demonstrate that only 60 per cent of the contents of the gall bladder are expelled by active muscular contractions of its wall, and McMaster and Elman state conservatively that "some portion of the gall bladder contents" is forcibly expelled by contraction of the viscus. Halpert<sup>3</sup> also calls attention to the fact that the largest amount of muscle is at the neck rather than at the fundus, a disposition which makes it hard to understand how forcible contractions of the fundus could force bile through the stronger muscle at the neck. He also points to the monkey, an animal in which the gall bladder is normally embedded in the liver, as a type in which it is impossible to see how strong intrinsic contractions could occur. (Fig. 63 and 64.) Moreover, certain of our own experiments seem to argue very

<sup>1</sup> Copher, Glover H., Kodama, S. and Graham, Evarts A.: The Filling and Emptying of the Gall Bladder, *Jour. Exper. Med.*, 1926, **44**, 65.

<sup>2</sup> Hamrick, R. A.: The Emptying of the Gall Bladder: An Experimental Study, *Am. Jour. Med. Sci.*, 1927, **174**, 168.

<sup>3</sup> Halpert, B.: Morphological Studies on the Gall Bladder: 1. A Note on the Development and the Microscopic Structure of the Normal Human Gall Bladder, *Bull. Johns Hopkins Hosp.*, 1927, **40**, 390.



strongly against contractions which could be effective in entirely emptying the organ. When the hepatic duct was ligated to prevent

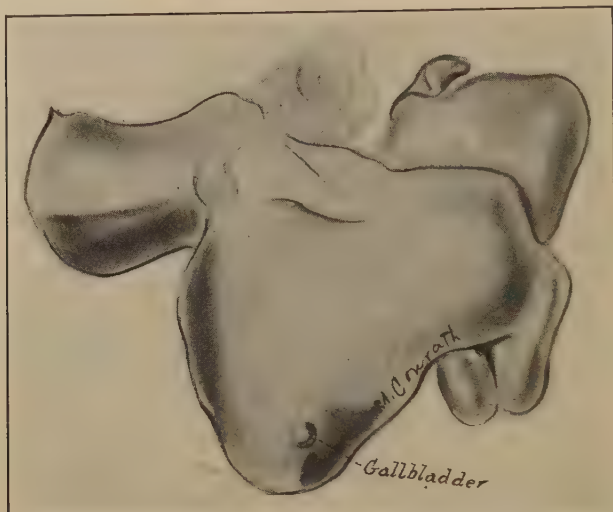


FIG. 63.—Liver and gall bladder of monkey. The gall bladder is seen projecting through the right lobe of the liver and appearing as a vesicle.



FIG. 64.—The same preparation seen in cross-section through the liver and gall bladder. In the monkey the gall bladder is normally embedded in the liver. It is difficult, therefore, to understand how strong muscular contractions could occur in the gall bladder of this animal.

access of bile to the gall bladder, the shadow remained for many days in spite of the ingestion of food (egg-yolk and cream), which

is supposed to incite contractions sufficiently strong to empty the gall bladder within a few hours. Our own opinion is that intrinsic contractions of the muscle occur but that they are not alone responsible for emptying the gall bladder of its contents. In this belief we are in accord also with Burget and with Carlson. We believe that the mechanism of emptying is a complex one, in which other factors, such as the washing out of the organ by fresh bile, the factor of elastic recoil, etc., play important rôles in addition to that played by the intrinsic muscular contractions.<sup>1</sup>

### VARIATIONS OF INTRA-ABDOMINAL PRESSURE.

Variations of intra-abdominal pressure due to respiratory movements, contiguous organs, etc., is doubtless a factor of minor importance in the emptying of the gall bladder. Winkelstein and Aschner<sup>2</sup> doubtless placed too much importance on this factor when they concluded that respiration is the "motor of the gall bladder." They found that increased intra-abdominal pressure arising from the inspiratory phase of respiration effects a large variation of pressure within the gall bladder and almost none in the common duct. The increased pressure due to respiration was thought to expel the bile from the gall bladder. These workers found bile in the common duct under a pressure of 60 to 70 mm. of bile. The closed sphincter of Oddi presented a resistance of 120 to 130 mm. of saline, and the cystic duct offered the slight resistance of 30 mm. Under these circumstances the gall bladder would fill with bile. At inspiration the pressure in the gall bladder was found to rise to 100 mm. or over, which would be sufficient to drive some bile from the gall bladder and common duct into the duodenum. A gross contractile emptying of the gall bladder was never observed. These observations of Winkelstein and Aschner indicate that increased abdominal pressure does not spread equally throughout the abdomen and therefore would become unimportant, but that the same factor produces

<sup>1</sup> In a recent article Boyden (Concerning the Prevalent Denial of Functions Long Attributed to the Gall Bladder, *Surg., Gynec. and Obst.*, 1928, **46**, 30) has summarized the arguments in favor of the idea that the gall bladder empties solely by contractions.

In another recent article Copher and Illingworth (Mechanism of Emptying of the Gall Bladder and Common Duct, *Surg., Gynec. and Obst.*, 1928, in press) have produced additional evidence that the gall bladder may show intrinsic contractions, but they also call attention to the importance of other factors in the mechanism of emptying. These authors have also observed peristaltic contractions of the common bile-duct in pigeons.

<sup>2</sup> Winkelstein, A. and Aschner, P. W.: Experimental Studies on the Color of the Bile from the Gall Bladder and Liver, *Am. Jour. Med. Sci.*, 1925, **169**, 842; The Mechanism of the Flow of Bile from the Liver into the Intestines: Conclusions from Previous Studies, *Am. Jour. Med. Sci.*, 1926, **171**, 104.

different pressure changes within different structures, depending on their size, shape, outlets, content, etc. Haberland<sup>1</sup> believes that the emptying of the gall bladder is largely a passive action due to pressure from nearby organs.

This conclusion differs from the one by McMaster and Elman, who noted fluctuations in the pressure within the biliary tract due to respiratory movements, but concluded that these pressure alterations affected not only the gall bladder, but the duodenum which might receive bile from it. They thought therefore, that a flow of bile could not occur under these circumstances.

Likewise, Whitaker<sup>2</sup> has questioned the possibility of extrinsic pressure being a factor in the emptying of the gall bladder. He concluded that hydrostatic conditions in the abdomen theoretically prevent the gall bladder emptying by outside pressure, because all of the abdominal contents have approximately the same specific gravity. However, Graham<sup>3</sup> has pointed out that if Whitaker's theory were correct, it would be impossible for the blood to circulate through the abdomen, because each pulse wave would be counteracted by transfer of the pressure to a point beyond the wave, which would nullify the pulse.

Copher<sup>4</sup> measured the pressures in the gall bladder, the common duct and a segment of the duodenum. There were fluctuations with respiratory movements. The pressure in the gall bladder averaged somewhat higher than in the common duct and duodenum. Potter and Mann, also, found the pressure greater in the gall bladder than in the duct. The average water pressure in the gall bladder was 141 mm. and 117 mm. in the duct. These findings indicate that it is possible for pressures within organs in the abdomen to vary.

Copher found that the size of a gall bladder of a dog, as shown by a cholecystogram, could be reduced by deep abdominal palpation. In other experiments concerning the effect of respiration on the emptying of the gall bladder, the right phrenic nerve of dogs was cut low in the neck and the lower portion removed by twisting in order to paralyze the diaphragm on that side. Cholecystograms in these dogs were delayed slightly in appearing and disappearing. The results from these experiments indicate that intra-abdominal

<sup>1</sup> Haberland, H. F. O.: *Der Entleerungsmechanismus der Gallenblase*, München, med. Wehnschr., 1926, **73**, 1969.

<sup>2</sup> Whitaker, L. R.: *The Mechanism of the Gall Bladder*, Am. Jour. Physiol., 1926, **78**, 411.

<sup>3</sup> Graham, Evarts A.: *The Present Status of Cholecystography and Remarks on the Mechanism of Emptying of the Gall Bladder*, Surg., Gynec. and Obst., 1927, **44**, 153.

<sup>4</sup> Copher, Glover H.: Unpublished work.

pressure may aid at times in the emptying of the gall bladder, though they are not essential for the process. Higgins and Mann, also, have arrived at the conclusion that intra-abdominal pressure is not a major factor in the emptying of the gall bladder on the basis of their observations of the response of the gall bladder in different species of animals to a diet rich in fat. Barsony and Koppenstein,<sup>1</sup> also, believe that intra-abdominal pressure has no effect on the emptying of the gall bladder.

### ABSORPTION THROUGH THE WALL OF THE GALL BLADDER.

Another manner of emptying the gall bladder is by absorption of a portion of its content through its walls. This process has been discussed under the heading, "Concentration of Bile in the Gall Bladder."

### RECIPROCAL ACTIVITY OF THE GALL BLADDER AND THE COMMON DUCT SPHINCTER.

The hypothesis, that the gall bladder contracts and the sphincter of the common duct relaxes simultaneously, has engaged the attention of many experimental and clinical investigators. Regardless of the many contributions, however, investigators do not agree in their findings relating to the combined activities of the gall bladder and the common duct sphincter. Since there is no unanimity of opinions, some of the results obtained for and against the presence of this physiological law will be discussed.

A simultaneous contraction of the gall bladder and relaxation of the duct sphincter was first said to have been noted by Doyon.<sup>2</sup> Rost<sup>3</sup> observed a relationship of the two activities. Meltzer<sup>4</sup> discussed disturbances of the law of contrary or crossed innervation of the gall bladder and the sphincter as a pathological factor in diseases of the biliary tract.

A diagnostic and therapeutic application of Meltzer's "law of

<sup>1</sup> Barsony, T. and Koppenstein, E.: Wird die Gallenblase durch die Bauchpresse entleert? München. med. Wehnschr., 1926, **73**, 1478.

<sup>2</sup> Doyon, M.: De l'action exercée par le système nerveux sur l'appareil excréteur de la bile, Arch. de physiol. noun. et path., 1894, **6**, 19.

<sup>3</sup> Rost, F.: Die funktionelle Bedeutung der Gallenblase; Experimentelle und Anatomische Untersuchungen nach Cholecystektomie Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, **26**, 710.

<sup>4</sup> Meltzer, S. T.: The Disturbance of the Law of Contrary Innervation as a Pathogenetic Factor in the Diseases of the Bile Ducts and Gall Bladder, Am. Jour. Med. Sci., 1917, **153**, 469.



innervation" was made by Lyon<sup>1</sup> in his "non-surgical drainage" of the biliary tract. He perfected a technique of duodenal lavage, by a tube *in situ*, with a solution of magnesium sulphate which, according to Meltzer, will cause a relaxation of the common duct sphincter and a simultaneous contraction of the gall bladder. By reason of this physiological mechanism, bile begins to flow through the tube and follows a sequence of color changes. The first, according to Lyon, the "A" bile is light golden-yellow and represents bile from the common duct and duodenum mixed with duodenal contents. Normally this is followed by the drainage of about 75 cc. of a brown or greenish-brown bile, so-called "B" bile, from the gall bladder. After all the dark-colored bile has been obtained, a quantity of light-golden-colored "C" bile comes through the tube. This, Lyon believes is the freshly secreted hepatic bile. Lyon's procedure is discussed again in Chapter V.

There has been considerable criticism of this theory and its practicability by able investigators, with evidence against it which is, to say the least, suggestive. On the other hand other observers uphold Lyon's contentions of the theory of the physiological mechanism purported to be involved, and of its practical clinical importance. Sachs,<sup>2</sup> Pribram<sup>3</sup> and Matsuo,<sup>4</sup> report that during the course of a laparotomy, they have seen the gall bladder expel its contents as a result of intraduodenal administration of magnesium sulphate and peptone. Silverman and Menville,<sup>5</sup> Eberhard<sup>6</sup> and Comstock<sup>7</sup> have found a decrease in the size of cholecystograms in response to intra-duodenal administration of magnesium sulphate. Copher and Moore<sup>8</sup> were unable to verify the latter observation.

Reports on the experimental work concerned with a reciprocal innervation of the gall bladder and the common duct sphincter are likewise not in agreement. Winkelstein and Aschner<sup>9</sup> were unable to prove Meltzer's theory of contrary innervation by the placing of

<sup>1</sup> Lyon, B. B. V.: *Non-surgical Drainage of the Gall Tract*, Philadelphia, 1923, Lea & Febiger, publishers.

<sup>2</sup> Sachs, Adolph: *Lyon-Meltzer Gall Bladder Drainage*, Nebraska Med. Jour., 1921, **6**, 225.

<sup>3</sup> Pribram, E. E.: *Peptone Gall Bladder Reflex*, Klin. Wehnschr., 1923, **2**, 1590.

<sup>4</sup> Matsuo, I.: *Magnesium Sulphate as a Cause of the Evacuation of the Gall Bladder*, Jour. Am. Med. Assn., 1924, **83**, 1289.

<sup>5</sup> Silverman, D. N. and Menville, L. J.: *Observations of the Visualized Gall Bladder by Graham Method*, Jour. Am. Med. Assn., 1925, **84**, 416.

<sup>6</sup> Eberhard: Quoted by Lyon, B. B. V., Jour. Am. Med. Assn., 1925, **85**, 1541.

<sup>7</sup> Comstock: *Ibid*.

<sup>8</sup> Copher, G. over H. and Moore, Sherwood: *Unpublished work*.

<sup>9</sup> Winkelstein, A. and Aschner, P. W.: *The Mechanism of the Flow of Bile from the Liver into the Intestines, Conclusions from Previous Studies*, Am. Jour. Med. Sci., 1926, **171**, 104.



methylen blue in the gall bladder and lavaging the duodenum with magnesium sulphate. Gantt and Volborth<sup>1</sup> were not able to note any effect of magnesium sulphate on the expulsion of bile into the duodenum.

The pressures in the gall bladder and the common duct of normal intact dogs were measured by Potter and Mann.<sup>2</sup> They found rhythmic waves of pressure in the gall bladder and the common duct. The findings of Copher and Kodama<sup>3</sup> make it probable that the large waves of pressure changes found in the common duct by Potter and Mann, are due to regulation of the flow of bile at the distal end of the common duct by the duodenum. Potter and Mann, also, found that the curve of pressure in the gall bladder rises as that in the common duct falls, after which the curves meet to separate again in the same manner. They found the pressure in the gall bladder might be higher than that in the common bile duct. These findings suggested to the experimenters that if the fall in pressure in the common duct was due to the opening of the sphincter of the duct and the rise of pressure in the gall bladder due to contraction of its musculature, Meltzer's law of reciprocal innervation is true.

A study of the reciprocal activities of the gall bladder in the unanesthetized healthy and active dog were made by McMaster and Elman<sup>4</sup> with a special technique of intubation of the biliary tract. They found that always after taking food there was a sudden decrease in the resistance to the passage of bile into the intestine, which was accompanied by a synchronous increase in the pressure within the gall bladder. They concluded that "there would appear to be a reciprocal response on the part of the two structures to the one stimulus."

The emptying of the gall bladders of fishes, guinea-pigs and dogs was observed by Higgins and Mann.<sup>5</sup> They concluded that the "sphincter of the common duct is not a factor in emptying the vesicle, except that its relaxation permits the bile to pass to the duodenum under pressure incited by the contraction of the gall bladder."

<sup>1</sup> Gantt, W. H. and Volborth, G. V.: The Influence of Magnesium Sulphate on the Expulsion of Bile from the Gall Bladder, *Jour. Lab. and Clin. Med.*, 1926, **11**, 542.

<sup>2</sup> Potter, J. C. and Mann, F. C.: Pressure Changes in the Biliary Tract, *Am. Jour. Med. Sci.*, 1926, **171**, 202.

<sup>3</sup> Copher, Glover H. and Kodama, Shuichi: The Regulation of the Flow of Bile and Pancreatic Juice into the Duodenum, *Arch. Int. Med.*, 1926, **38**, 647.

<sup>4</sup> McMaster, P. D. and Elman, R.: On the Expulsion of Bile by the Gall Bladder; and a Reciprocal Relationship with the Sphincter Activity, *Jour. Exper. Med.*, 1926, **44**, 173.

<sup>5</sup> Higgins, G. M., and Mann, F. C.: Observations on the Emptying of the Gall Bladder, *Am. Jour. Physiol.*, 1926, **78**, 389.

An intermittent nature of the contraction and filling of the gall bladder was found by Boyden.<sup>1</sup> These phases seemed closely correlated with the periodic action of the sphincter of the common duct.

Whitaker,<sup>2</sup> however, is doubtful if there is a reciprocal innervation or relationship between the common duct sphincter and the gall bladder. The gall bladder was found to function normally even though denervated, and the viscus did not empty after the sphincter was cut and dilated until the muscles of its walls were activated by the ingestion of protein or fat.

The effect of eliminating the sphincter of Oddi was investigated by Burget,<sup>3</sup> and he concluded that a reciprocal activity between the gall bladder and the sphincter that would influence the expulsion of bile is improbable.

The distal end of the common bile duct was divided at a point proximal to the sphincter and implanted into another part of the duodenum by Berg and Jobling.<sup>4</sup> The effect of the transplantation of the duct upon the gall bladder was studied by cholecystography. They were able to obtain normal cholecystograms after the procedure, and concluded that a reciprocal relationship of the sphincter of Oddi and the gall bladder does not exist.

Copher and Kodama<sup>5</sup> found changes of pressure in the duodenum, common duct and gall bladder that suggested a relationship of activities in response to a common stimulus. (Fig. 54.) They also found an increased pressure in the gall bladder with a simultaneous relaxation of the sphincter after the injection of adrenalin. Later experiments in which an artificial rubber gall bladder was used *in vivo*, revealed that a forceful contraction due to a muscular action of the wall of the gall bladder is probably not necessary for the emptying of the viscus. The cycle of shadows produced by the artificial rubber gall bladder after injection of tetraiodophenolphthalein was quite like that obtained from the normal gall bladder of the human, except that the shadows were not so dense and that

<sup>1</sup> Boyden, E. A.: A Study of the Behavior of the Human Gall Bladder in Response to the Ingestion of Food; Together with Some Observations on the Mechanism of the Expulsion of Bile in Experimental Animals, *Anat. Rec.*, 1925, **33**, 201.

<sup>2</sup> Whitaker, L. R.: The Mechanism of the Gall Bladder and its Relation to Cholelithiasis, *Jour. Am. Med. Assn.*, 1927, **88**, 1542.

<sup>3</sup> Burget, G. E.: Regulation of Flow of Bile: II. Effect of Eliminating Sphincter of Oddi, *Am. Jour. Physiol.*, 1926, **79**, 130.

<sup>4</sup> Berg, B. N. and Jobling, J. W.: The Effect of Division and Transplantation of the Common Duct upon Gall Bladder Function, *Proc. Soc. for Exper. Biol. and Med.*, 1927, **24**, 434.

<sup>5</sup> Copher, Glover H. and Kodama, Shuichi: The Regulation of the Flow of Bile and Pancreatic Juice into the Duodenum, *Arch. Int. Med.*, 1926, **38**, 647.

they persisted over a longer time. This experiment seems to prove that the gall bladder may empty without the presence of a reciprocal innervation of the gall bladder and the common duct sphincter.

### INFLUENCE OF THE NERVE SUPPLY OF THE GALL BLADDER.

The conclusions regarding the functions of the nerve supply to the gall bladder are conflicting. Bainbridge and Dale,<sup>1</sup> Chiray and Pavel,<sup>2</sup> Courtade and Guyon,<sup>3</sup> Lieb and McWhorter,<sup>4</sup> Westphal,<sup>5</sup> and others have concluded that the vagus is the motor nerve to the gall bladder. The opinion that the vagus is not the motor nerve to the gall bladder is held by Auster and Crohn,<sup>6</sup> Doyon,<sup>7</sup> Winkelstein and Aschner<sup>8</sup> and others. These and other workers likewise do not agree regarding the function of the splanchnics. Mann,<sup>9</sup> nevertheless, has concluded that the vagus is mainly motor and the splanchnic mainly inhibitory to the gall bladder. This conclusion, which Freese<sup>10</sup> and others had arrived at some time before, that all of the motor and inhibitory fibers do not run in the same nerves, is seemingly true for the other organs of the body.

The advent of a means of visualizing the intact gall bladder in the living animal has permitted further investigation of the function of the nerve supply to the gall bladder. This method seems to be one of the most accurate of those used. The effect of nerve stimulation on the emptying of the gall bladder of normal animals studied by roentgenograms was first reported by Whitaker.<sup>11</sup> He concluded after electrical stimulation of either vagus, both centrally

<sup>1</sup> Bainbridge, F. A. and Dale, H. H.: The Contractile Mechanism of the Gall Bladder and its Extrinsic Nervous Control, *Jour. Physiol.*, 1905, **33**, 138.

<sup>2</sup> Chiray, M. and Pavel, I.: La contractilite de la vesicule biliaire, ler memoire: etude critique, *Jour. de physiol. et de Path. Gen.*, 1925, **23**, 105.

<sup>3</sup> Courtade, D. and Guyon, J. F.: Action motrice du pneumogastrique sur la vesicule biliaire, *Compt. rend. Soc. de biol.*, 1904, **56**, 313.

<sup>4</sup> Lieb, C. C. and McWhorter, J. E.: Action of Drugs on the Isolated Gall Bladder, *Jour. Pharmacol. and Exper. Therap.*, 1915, **7**, 83.

<sup>5</sup> Westphal, Karl: Muskelfunktion, Nervensystem u. Pathologie der Gallenwege. I. Untersuchungen über den Schmerzanfall der Gallenwege und seine Ausstrahlenden Reflexe, *Ztschr. f. klin. Med.*, 1923, **96**, 22.

<sup>6</sup> Auster, L. S. and Crohn, B. B.: Notes on Studies in the Physiology of the Gall Bladder, *Am. Jour. Med. Sci.*, 1922, **164**, 345.

<sup>7</sup> Doyon, M.: Mouvements spontanés des voies biliaires, *Arch. de Physiol. noun. et path.*, 1893, **5**, 710.

<sup>8</sup> Winkelstein, A. and Aschner, P. W.: The Mechanism of the Flow of Bile from the Liver into the Intestines, Conclusions from Previous Studies, *Am. Jour. Med. Sci.*, 1926, **171**, 104.

<sup>9</sup> Mann, F. C.: The Functions of the Gall Bladder, *Physiol. Rev.*, 1924, **4**, 251.

<sup>10</sup> Freese, J. A.: The Force of Contraction of the Gall Bladder and the Course of its Motor and Inhibitory Nerve Fibers, *Bull. Johns Hopkins Hosp.*, 1905, **16**, 235.

<sup>11</sup> Whitaker, L. R.: The Mechanism of the Gall Bladder, *Am. Jour. Physiol.*, 1926, **78**, 411.

and peripherally, and after drug stimulation, that the vagus and splanchnic nerves play no essential rôle in the emptying of the gall bladder, which was made opaque to the roentgen-ray by direct injection into the gall bladder of iodized oil. The gall bladder seemed to function normally after the vagi and splanchnics were cut.

A marked ability of adrenalin to produce a diminution in size of the gall bladder which was noted by Boyden and interpreted by him as a muscular contraction, seemed to him to prove a partial nervous control of the organ at least by the sympathetic system. This observation with other ingenious experiments made him favor the view that the gall bladder is controlled both by nerves in the splanchnic trunks and by hormones in the circulating blood. However, if adrenalin produces a contraction of the muscle of the gall bladder, this action is at variance with its well known effects on the smooth muscle of other similar organs. Indeed, Burget<sup>1</sup> has suggested that the apparent contraction of the gall bladder induced by adrenalin is after all probably due to a relaxation of the duodenum which in turn permits the gall bladder to become diminished in size by the escape of some of its bile into the intestine. It is of interest here that in other experiments Copher and Kodama<sup>2</sup> found that adrenalin reduced to a minimum the pressure in the common bile-duct which would be withstood by the mechanism controlling the distal end of the common duct, indicating therefore a relaxation of its end as suggested by Burget. Several other drugs which raise the blood-pressure cause a rapid disappearance of the shadow of the gall bladder, indicating that, like adrenalin, they all cause a relaxation of the lower end of the common duct.

Copher and Kodama independently studied the question of the function of the extrinsic nerves of the gall bladder. In their experiments the roentgenographic study of the gall bladders of dogs was made after the intravenous injection of suitable dyes for visualizing the gall bladder. Neither short or prolonged, gentle or violent, nor central or peripheral electrical stimulation of either vagus nerve seemed to influence the emptying of the gall bladder. If the left vagus nerve was sectioned in the neck at the time of the injection of dye, there was often a delay in the appearance and disappearance of the shadow of the gall bladder. The shadow, instead of reaching its maximum density in twenty-four hours, which it normally would do in dogs, usually did not reach that stage for forty-eight hours.

<sup>1</sup> Burget, G. E.: The Regulation of the Flow of Bile. III. The Rôle of the Gall Bladder, *Am. Jour. Physiol.*, 1927, **81**, 422.

<sup>2</sup> Copher, Glover H. and Kodama, S.: Unpublished work.



There were no definite alterations in the cycle after sectioning of the right vagus nerve.

Shadows were obtained after the right and left vagi were cut. In this instance there was some delay in the appearance and disappearance of the shadow similar to that found after section of the left vagus nerve alone. The shadows of the gall bladder after section of the vagi were sometimes larger, as if they were distended, than one would expect. Although these experiments of Copher and Kodama suggest some control of the vagi, particularly the left vagus, over the gall bladder, the results are questionable.

Copher and Kodama were also unable to arrive at definite conclusions regarding the control of the sympathetic nervous system over the gall bladder.

Pituitrin has been found by many investigators to cause a rapid disappearance of the shadow of the gall bladder. Its action, whether by stimulation of smooth muscle or through some nervous control, has not been proven. Perhaps its action is like that of adrenalin discussed above.

Although all of these experiments strongly indicate that the extrinsic nerves have something to do with the normal functioning of the gall bladder, further investigations are necessary to evaluate properly their importance. Although it is remarkable to find, that the gall bladder is capable of emptying after apparently a complete removal of extrinsic nerves, it may be not unlike the intestine, which will function by its intrinsic nervous system alone. An intrinsic nerve supply of the gall bladder has been described by Ischiyama,<sup>1</sup> who found a rich supply of ganglion cells which presumably constitute an autonomic system of the organ.

Seemingly, Vulpian<sup>2</sup> is the only investigator who has suggested that there may be present a medullary center for the gall bladder. Vulpian found in dogs that "piqûre" of the medulla constantly resulted in the filling of the duodenum with bile.

### FATS, LIPOIDS AND THE GALL BLADDER.

Though a considerable number of facts have been discovered concerning the relationship of the gall bladder to fats, fatty acids and lipoids, there remain many unestablished facts regarding them.

<sup>1</sup> Ischiyama, F.: Experimentelle Untersuchungen ueber die Funktion der Gallenblase bei der Gallenauscheidung in das Duodenum insbesondere ueber ein Hormone in der Gallenblasenwand und ueber den Wirkungswechsel von Adrenalin auf die Gallenblase, Mitt. a. d. Med. Fak. d. r. Univ. Kyushu, Fukuoka, 1925, 10, 61.

<sup>2</sup> Vulpian: Quoted from Doyon, M.: De l'action exercée par le système nerveux, sur l'appareil excréteur de la bile, Arch. de Physiol., 1894, 6, 19.



Many clinical observations have been made concerning the association between disease of the gall bladder and fat metabolism. Cholesterol is of especial interest because of its presence in gall stones.

Cholesterol is a monatomic alcohol and possesses some of the properties of fat. It is soluble in fat solvents and so is classed with the fat-like substances, the lipoids. Cholesterol, like other alcohols, forms combinations with acids called esters. It is present not only in bile, but also to some extent in all animal cells. Large amounts of bile salts and an alkaline reaction favor its solution. It goes into a colloidal solution as an emulsion. The endogenous origin of cholesterol is from erythrocytes, nervous tissue, etc., and its exogenous origin from food. Because of its presence in all cells it must have an important function of some kind, but up to the present time there is little exact knowledge as to what its function is. The solution of the problem of cholesterol metabolism is one of the great problems of the future. Investigators do not agree as to whether it is absorbed or is excreted by the epithelial cells of the mucous membrane of the gall bladder. Some believe it is a product of degeneration of these cells.

Virchow<sup>1</sup> suggested that fat is taken from the bile by the gall bladder wall, that it undergoes an intermediate metabolism in the wall and that it then passes into the circulation. Aschoff<sup>2</sup> showed that the gall bladder can take up neutral fat from the content of the gall bladder and traced it into the lymphatics. Policard<sup>3</sup> concluded that the gall bladder absorbs fat in a similar manner to the intestinal epithelium. Boyd<sup>4</sup> and others have concluded that cholesterol is one of the chief substances absorbed by the gall bladder. Sweet<sup>5</sup> reports that in the dog the total blood cholesterol increased as much as twice the normal after removal of the normal gall bladder. The blood cholesterol content reached the normal level forty days after operation and then fell below normal. There was also a delay of three hours in the increase of the blood cholesterol level after ingestion of fats following cholecystectomy. Mentzer<sup>6</sup> found the epi-

<sup>1</sup> Virchow, Rud.: Ueber das Epithel der Gallenblase und ueber einen intermediären Stoffwechsel des Fettes, *Arch. f. path. Anat. u. Physiol.*, 1857, **11**, 574.

<sup>2</sup> Aschoff, L.: Zur Frage der Cholesterinbildung in der Gallenblase, *München. med. Wehnschr.*, 1906, **53**, 1847.

<sup>3</sup> Policard, A.: Sur les phénomènes d'absorption au niveau de l'épithélium de la vésicule biliaire, *Compt. rend. de la Soc. de Biol.*, 1914, **76**, 338.

<sup>4</sup> Boyd, W.: Studies in Gall Bladder Pathology, *British Jour. Surg.*, 1922-1923, **10**, 337.

<sup>5</sup> Sweet, J. E.: The Gall Bladder: Its Past, Present and Future, *Internat. Clin.*, 1924, **50**, 187.

<sup>6</sup> Mentzer, S. H.: Cholesterosis of the Gall Bladder, *Am. Jour. Path.*, 1925, **1**, 383.

thelial cells of the mucosa of the gall bladder capable of absorbing highly emulsified fat particles as well as solid particles, such as powdered charcoal and India ink.

On the other hand, evidence has been offered by several that cholesterol is excreted by the mucosa.

### GALL-BLADDER HORMONE.

The possibility of the secretion of a hormone by the gall bladder has been considered. Such a hormone might influence the activity of the liver, the gall bladder, fat and cholesterol metabolism, etc. It has been mentioned by Graham that it is significant that the venous blood of the gall bladder flows directly into the portal vein instead of into the hepatic veins, as if something from the gall bladder might be useful in the metabolism of the liver.

A hormone of a choline-like nature has been found in the gall bladder by Ischiyama.<sup>1</sup> The presence of the hormone was found to alter the effect of adrenalin and to stimulate the activity of ganglion cells in the wall of the gall bladder.

Copher and Higgins,<sup>2</sup> independently, on the possibility that the gall bladder might secrete some substance that would influence the activity of the organ, made extracts from the gall bladders of dogs and cows by various extraction methods. There was no effect on the gall bladder of the dog by the intravenous injection of these extracts as determined by cholecystography.<sup>3</sup>

It has long been known that the mucosa of the gall bladder secretes mucus.<sup>4</sup>

<sup>1</sup> Ischiyama F.: *Ibid.*

<sup>2</sup> Copher, Glover H. and Higgins, C. K.: Unpublished work.

<sup>3</sup> Copher and Illingworth (Mechanism of Emptying of the Gall Bladder and Common Duct, Surg., Gynec. and Obst., 1928, in press) were unable to observe any effect of various preparations of secretin on the gall bladder; but Ivy and Oldberg (Proc. Soc. Exper. Biol. and Med., 1928, 35, p. 251) have recently reported a successful demonstration of contractions due to a substance closely related to secretin.

<sup>4</sup> Because of a typographical error, consisting of the omission of one important word in the published report of his McArthur Lecture, one of us (Graham: New Developments in our Knowledge of the Gall Bladder, Am. Jour. Med. Sci., 1926, 172, 625), has been repeatedly quoted as having the opinion that "the chief function of the gall bladder is to maintain tonus and to prevent over-distention." The printer's devil or some devil of a printer struck out the word "muscle" which should have followed "gall bladder." As originally written, therefore, the sentence read as follows: "We believe that the chief function of the gall bladder *muscle* is to maintain tonus and to prevent over-distention." In the light of all the evidence we are unwilling to subscribe to the opinion that the gall bladder itself plays merely a passive rôle which the misprint credited us as doing. On the contrary, we feel that it is highly probable that the gall bladder has a definite and perhaps important part in the metabolism of cholesterol, which will be more certainly revealed in the future.

**BEHAVIOR OF THE HUMAN GALL BLADDER DURING FASTING.**

During the early development of cholecystography, it was noted that it was necessary to have the patient fasting at the time of the administration of the halogenated phenolphthaleins, in order surely to visualize the normal gall bladder with the roentgen-ray. The normal gall bladder was found to pass through a characteristic cycle of changes while the patient was fasting. A large, faint shadow appeared on the film from three and one-half to five hours after the intravenous injection of tetraiodophenolphthalein to be followed by one of greater density and smaller size within the next few hours; the heaviest shadow appeared after about twelve to twenty-four hours. The patients were given food at the end of ten hours and the shadow disappeared in approximately thirty-six hours. The shadows produced by phenoltetraiodophthalein are the same except that the shadow has usually disappeared in twenty-four hours after intravenous injection. It was noted that if the patients were inadvertently given food at noon, after the injection of the dye in the morning, the shadow of the gall bladder promptly disappeared. The distended gall bladder seems to empty more rapidly after taking food than the partially empty one.

The volume of a human gall bladder during a fasting period decreases greatly coincidentally with hunger pains, according to Boyden.<sup>1</sup> He believes this observation confirms the opinion of Boldireff that bile from the gall bladder is discharged into the duodenum synchronously with contraction of the fasting stomach. Boyden suggests that it is possible that the contraction of the gall bladder may be associated with other functions than digestion.

**RESPONSE OF THE GALL BLADDER TO THE INGESTION OF FOOD.**

The secretion of bile, the mechanism of the emptying of the gall bladder and the regulation of the flow of bile by the sphincter of the common bile-duct are adjusted to meet efficiently the requirements of digestion. Although bile flows into the duodenum in the fasting state, the amount is greatly increased by the taking of food. Klodnizki<sup>2</sup> has shown that fats cause greater acceleration of the flow of bile from the liver than any other food. The yolk of

<sup>1</sup> Boyden, E. A.: Behavior of Human Gall Bladder during Fasting and in Response to Food, *Proc. Soc. Exper. Biol. and Med.*, 1926, **24**, 157.

<sup>2</sup> Klodnizki: Quoted by Babkin: *Die Aussere Sekretion der Verdauungsdrusen*, Berlin, 1914.

hen's egg was especially effective. While protein itself did not seem to be a stimulant for the passage of bile into the duodenum, products of protein digestion were active stimulants. Carbohydrates seemed to be the least active stimulant. The beginning of the secretion of bile did not coincide with the moment of feeding the animal. It occurred after a latent period, which varied with the sort of food fed, and the increased secretion of bile by the liver ended when the stomach was empty. The bile flowing in the first hour of digestion was richer in solids than later.

The first requirements of digestion for bile are met by the emptying of the gall bladder. Okada<sup>1</sup> noted that the rhythmic waves of the gall bladder of the anesthetized dog were increased in number when oil, food or hydrochloric acid was injected into the duodenum. Many other observations have been made regarding the flow of bile into the duodenum in response to food. An important observation on the emptying of the gall bladder was made by Boyden.<sup>2</sup> He noted in a large series of cats that the gall bladder emptied after a meal of lipoids and fats (egg-yolk and cream). Boyden<sup>3</sup> then demonstrated the existence in man of a functional cycle of the gall bladder similar to that in the cat. He found that the gall bladder of a cat passed from a fully distended to a nearly collapsed state in approximately one and three-fourths hours after a meal of egg-yolk and cream. The organ remained more or less collapsed for nearly five hours. During this resting period, although collapsed, it was never entirely empty because of the inflow of small amounts of bile from the liver as a result of the intermittent action of the sphincter papillæ. After the period of partial collapse of five hours, it commenced to distend and became fully distended about ten hours after the meal.

After investigating other foods and finding them not so effective in emptying the gall bladder, Boyden studied the action of the yolk of eggs by segregating and administering separately some of the substances of which it is composed. These substances were (1) the fats (olein, palmitin and stearin), (2) lipoids (lecithin), and (3) cholesterol. Lecithin was thought by Boyden to be the most effective of these substances.

Later results published in another paper fail to confirm the idea that lecithin is the specific substance in egg-yolk which produces

<sup>1</sup> Okada, S.: On the Secretion of Bile, *Jour. Physiol.*, 1914, **49**, 457.

<sup>2</sup> Boyden, E. A.: The Gall Bladder in the Cat, *Anat. Rec.*, 1922-1923, **24**, 388.

<sup>3</sup> Boyden, E. A.: The Effect of Natural Food on the Distension of the Gall Bladder, with a note on the Change in Pattern of the Mucosa as it Passes from Distension to Collapse, *Anat. Rec.*, 1925, **30**, 333.



nearly complete emptying of the gall bladder. Superimposed feeding of heavy cream given to cats at two-hour intervals failed to be more effective in emptying the gall bladder than a single dose, which about half collapsed the viscus. This experiment indicated that a difference in the quantity of fat is not a factor in its effectiveness. Boyden transfused arterial blood of a cat that had been digesting egg-yolk for one and a half hours, into the veins of a fasting cat whose gall bladder had been previously filled with iodized oil. Considerable amounts of iodized oil appeared in the duodenum, indicating that the blood from the cat recently fed egg-yolk contained substances that activated the gall bladder. However, marked contractions of the gall bladder also followed the transfusion of blood from a fasting animal to a test cat. Auto-transfusion was then found to cause an expulsion of bile into the cystic duct. In other experiments relating to the hormone control of the gall bladder, the lacteal trunks in the mesenteries of the cats were ligated, and the gall bladder still contracted the next day after ingestion of egg-yolks. Similar experiments were performed, except that the portal vein was ligated instead of the lacteals. A weak contraction of the gall bladder was then obtained. These experiments indicate that the ingestion of food may activate the gall bladder even though its absorption by the veins or the lymphatics is prevented, and argue against an exclusive hormonal control of the gall bladder. Boyden has concluded from later experiments that the mechanical passage of food through the intestinal tract is not a factor in the emptying of the gall bladder.

A study of the contraction curve of the gall bladder by Boyden showed it to be intermittent. The short latent period before contraction of the gall bladder after ingestion of egg-yolk suggests that the bile in the viscus is used for the early part of digestion, and bile in the liver for later stages. Meat did not completely empty the gall bladder

Apparently, Sosman, Whitaker and Edson<sup>1</sup> were the first to utilize cholecystography as a means of observing the normal reaction of the human gall bladder to various stimuli. The sight, smell or taste of food had no effect on the size of the gall bladder visualized by cholecystography. Ingestion of food rich in fats nearly always caused the disappearance of the shadow in from three to six hours. Protein and peptone caused a moderate decrease in the size of the shadow and carbohydrates were given without any effect.

<sup>1</sup> Sosman, M. C., Whitaker, L. R. and Edson, P. J.: Clinical and Experimental Cholecystography, *Am. Jour. Roentgenol.*, 1925, **14**, 495.

Observations made by Higgins and Mann<sup>1</sup> on the emptying of the gall bladder of fishes, amphibia, birds and mammals after a diet rich in fat, confirm the results of Boyden.

Copher,<sup>2</sup> also, has studied the effect of food after the method of Boyden and Whitaker and has confirmed their finding of the marked ability of fats to empty the gall bladder. He has called attention to the fact that the gall bladder of the dog apparently may never completely empty, even though the animal is fed its usual diet. For example, if a daily injection of tetraiodophenolphthalein is given to dogs, shadows of the gall bladders are continuously present even when the animals are allowed their usual freedom and are fed liberal amounts of a mixed diet of fat, protein and carbohydrate. The shadows of the gall bladder varied somewhat in size and shape, but were always present. Several other investigators have made the observation that the gall bladder apparently is never entirely empty. Boyden found that the gall bladder of cats, although collapsed, is never entirely empty, because of the inflow of new bile and the concentrating activity of the wall. Potter and Mann<sup>3</sup> state that "it is apparent that the gall bladder does not contract completely." Mann, later, with Higgins<sup>4</sup> studied the effect of egg-yolk and cream on the surgically exposed gall bladder of fasting animals. The gall bladder was never found entirely empty of bile, although they had found it so in sacrificed animals. They concluded that the complete emptying of the vesicle was prevented by the experimental procedures. McMaster and Elman,<sup>5</sup> in their determination of pressures in the biliary tract of the unanesthetized dogs, found only a partial emptying of the gall bladder.

### EFFECT OF DRUGS ON THE ACTION OF THE GALL BLADDER.

The effect of drugs on the human gall bladder was studied by Sosman, Whitaker and Edson.<sup>6</sup> Neither olive nor castor oil produced any effect on the gall bladder. Magnesium sulphate given by duodenal tube caused a moderate decrease in the size

<sup>1</sup> Higgins, G. M. and Mann, F. C.: Observations on the Emptying of the Gall Bladder, *Am. Jour. Physiol.*, 1926, **78**, 339.

<sup>2</sup> Copher, Glover H.: Unpublished work.

<sup>3</sup> Potter, J. C. and Mann, F. C.: Pressure Changes in the Biliary Tract, *Am. Jour. Med. Sci.*, 1926, **171**, 202.

<sup>4</sup> Higgins, G. M. and Mann, F. C.: Observations on the Emptying of the Gall Bladder, *Am. Jour. Physiol.*, 1926, **78**, 339.

<sup>5</sup> McMaster, P. D. and Elman, R.: On the Expulsion of Bile by the Gall Bladder, and a Reciprocal Relationship with the Sphincter Activity, *Jour. Exper. Med.*, 1926, **44**, 173.

<sup>6</sup> Sosman, M. C., Whitaker, L. R. and Edson, P. J.: Clinical and Experimental Cholecystography, *Am. Jour. Roentgenol.*, 1925, **14**, 495.

of the shadow. The action of magnesium sulphate on the biliary tract is more fully discussed in the section on the reciprocal action of the gall bladder and the common duct sphincter. Sodium bicarbonate by mouth produced a slight increase in the size of the shadow with a decrease in density. Hypodermic injections of atropine sulphate, physostigmin, pilocarpin, pituitrin and adrenalin, and dilute hydrochloric acid, nitroglycerin, meat extracts, ginger, starch glucose and alcohol given by mouth did not have a constant effect on the size or density of the gall bladder shadow.

Intravenous injection of barium chloride and cholin hydrochloride were found by Boyden<sup>1</sup> to produce contractions of the gall bladder and expulsion of iodized oil from the gall bladder.

Atropine sulphate, which supposedly relaxes the common duct sphincter, was found by Whitaker<sup>2</sup> to reduce markedly the rate of emptying of the gall bladder, presumably by its action on the musculature of the gall bladder.

Ergotamin is said by Campanacci and Groppali<sup>3</sup> to cause a great increase in the flow and concentration of bile. They suggest its clinical use for this purpose.

#### EFFECT OF EXTRACTS OF GLANDS OF INTERNAL SECRETION ON THE ACTION OF THE GALL BLADDER.

Investigators of physiology of the gall bladder soon after the discovery of cholecystography studied the effect of internal secretions on the action of the gall bladder. Sosman, Whitaker and Edson<sup>4</sup> were unable, as were Copher and Higgins,<sup>5</sup> to find a marked effect after intravenous injections of large doses of secretin prepared by the method of Bayliss and Starling. No effect was secured by the application of hydrochloric acid to the duodenal mucosa, which presumably causes the production of secretin. Intravenous injection of adrenalin chloride produces a rapid disappearance of the shadow of the gall bladder. Boyden observed its action in cats, and Copher found in dogs that not only does it produce an increase of pressure in the gall bladder, but the common duct sphincter is simultaneously relaxed. This action of adrenalin indicates that the

<sup>1</sup> Boyden, E. A.: The Gall Bladder in the Cat, *Anat. Rec.*, 1922-1923, **24**, 388.

<sup>2</sup> Whitaker, L. R.: The Mechanism of the Gall Bladder, *Am. Jour. Physiol.*, 1926, **78**, 411.

<sup>3</sup> Campanacci, G. and Groppali, M.: Beitrag zur Motilität der Gallenblase (Ergotaminreflex), *Klin. Wchnschr.*, Berlin, 1926, **5**, 1639.

<sup>4</sup> Sosman, M. C., Whitaker, L. R. and Edson, P. J.: Clinical and Experimental Cholecystography, *Am. Jour. Roentgenol.*, 1925, **14**, 495.

<sup>5</sup> Copher, Glover H. and Higgins, C. K.: Unpublished work.

sympathetic nervous system supplies motor fibers to the gall bladder. Boyden found that the intravenous injection of heparin stimulates the gall bladder to contract. Copher and Higgins<sup>1</sup> investigated the action of insulin and parathyroid hormone (Collip). Neither of them produced a marked contraction of the gall bladder. Kaznelson and Reimann,<sup>2</sup> and Pribram, Gruenberg and Strauss,<sup>3</sup> Kalk and Schondube<sup>4</sup> and Chiray, Lekon and Callegari<sup>5</sup> have made an exhaustive study of the ability of pituitrin to produce an active contraction of the gall bladder. Brugsch and Horsters,<sup>6</sup> however, believe that pituitary extract causes a relaxation of the gall bladder and a contraction of Oddi's sphincter.

### INFLUENCE OF CHOLAGOGUES ON THE GALL BLADDER.

The effect of cholagogues on the gall bladder has been studied. Pribram,<sup>7</sup> on the basis that cincophen is a choloretic, used diiodo-cincophen for cholecystography. Spurling and Hartman<sup>8</sup> studied the choloretic action of neocinchophen (ethyl ester of para-methyl-phenyl-cinchonic acid) for reducing the time normally necessary for the production of cholecystographic shadows. They found that the time for the attainment of maximum density of the shadow could be reduced approximately one-half by the oral administration of 1 gm. of neocinchophen one hour prior to the intravenous injection of tetraiodophenolphthalein. Copher, Woodmansee and Moore<sup>9</sup> have confirmed the findings of Spurling and Hartman, but have not found it desirable to make clinical application of the fact. The action of neocinchophen seems to depend almost entirely on its choloretic action, rather than upon any action upon the gall bladder

<sup>1</sup> Copher, Glover H. and Higgins, C. K.: Unpublished work.

<sup>2</sup> Kaznelson, P. and Reimann, F.: Erfahrungen ueber die roentgenologische Darstellung der Gallenblase mittels Tetrabromphenolphthalein nach Graham-Cole, *Klin. Wehnschr.*, 1925, **4**, 1390.

<sup>3</sup> Pribram, B. D., Gruenberg, K. and Strauss, O.: Die roentgenologische Darstellung der Gallenblase und ihre klinische-praktische Bedeutung, *Deutsch. med. Wehnschr.*, 1925, **51**, 429.

<sup>4</sup> Kalk, H. and Schondube, W.: Ueber die Funktion der Gallenblase, Untersuchungen an Normalen an Hand der Pituitrin—bzw. Hypophysinprobe—*Ztschr. f. d. ges. exp. Med.*, 1926, **53**, 461.

<sup>5</sup> Chiray, M., Lekon, J. and Callegari, H.: Action of Certain Stimulants of Vegetative and Endocrine Systems on Contraction of Gall Bladder in Man, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1926, **50**, 103.

<sup>6</sup> Brugsch, T. and Horsters, H.: Cholecystography, *Med. Klin.*, Berlin, 1926, **22**, 1174.

<sup>7</sup> Pribram, B. D.: New Contrast Substance for Cholecystography, *Deutsch. med. Wehnschr.*, 1926, **52**, 1291.

<sup>8</sup> Spurling, R. G. and Hartman, E. E.: Choloretic Action of Tolysin (Ethyl Ester of Para-methyl-phenylcinchonic Acid) in Cholecystography, *Jour. Pharmacol. and Exper. Ther.*, 1926, **30**, 101.

<sup>9</sup> Copher, Glover H., Woodmansee and Moore, Sherwood: Unpublished work.



musculature. The toxic effects of these substances have led to their complete abandonment in cholecystography by Pribram and others.

Bile salts, which are said to be effective cholagogues, have been used by Copher, Woodmansee and Moore in an attempt to reduce the time necessary for cholecystographic examination. They were not satisfactory for this purpose. Whitaker found that bile salts, instead of contracting the gall bladder, seemed to distend it. Levinson,<sup>1</sup> however, finds that the size of a gall bladder shadow may be made to decrease rapidly by the administration of bile salts combined with oleic acid.

#### EFFECT OF MISCELLANEOUS FACTORS ON THE ACTION OF THE GALL BLADDER.

No effect from exercise in which the abdominal muscles were used strenuously was found by Sosman, Whitaker and Edson on the gall bladder shadow of students. Copher was able to decrease considerably the size of the shadow of the gall bladder by vigorous massage and palpation of the upper abdominal wall of dogs. Heat and cold applied to the abdominal wall had no effect on the shadow. The sensitiveness of the gall bladder to various stimuli, other than food, has been noted by Boyden. He found that the gall bladder of cats contracted after blood transfusion and after shaving the extremity, cutaneous incisions, etc. Whitaker noted that the physical condition of the experimental animals is an important factor in determining the reactivity of the gall bladder to stimuli. Emptying may not occur if the animal is ill. Trauma of the wall of the gall bladder interferes with its emptying. Kalk and Schondube<sup>2</sup> found the gall bladder in the pregnant female to contract earlier and more suddenly after injection of pituitrin than in the non-pregnant woman. There was also found a stasis of the contrast media in the gall bladder during pregnancy.

#### ANATOMICAL AND FUNCTIONAL PHYSIOLOGICAL VARIATIONS OF THE NORMAL GALL BLADDER.

Soon after the advent of the means of visualizing the normal human gall bladder by cholecystography, Sherwood Moore<sup>3</sup> sug-

<sup>1</sup> Levinson, Bernard: Biliary Tract Disease: A New Method of Treatment, *Med. Jour. and Rec.*, 1927, **255**, 801.

<sup>2</sup> Kalk, H. and Schondube, W.: Über die Funktion der Gallenblase. Untersuchungen an Normalen an Hand der Pituitrin—bzw. Hypophysinprobe—*Ztschr. f. d. ges. exper. Med.*, 1926, **53**, 461.

<sup>3</sup> Moore, Sherwood: Cholecystography, after the Method of Graham, Cole and Copher, *Am. Jour. Roentgenol and Rad. Ther.*, 1925, **13**, 515.

gested that the relationship of bodily habitus to the form, function and tonus of the alimentary canal, as observed by Mills,<sup>1</sup> might apply with equal force to the gall bladder. The anatomical variations of the gall bladder were found to coincide in general with the individual's habitus. For example, the asthenic patient should typically show a long, narrow gall bladder in a low position in the abdomen, whereas the sthenic individual should show a shorter, wider gall bladder under the costal margin. Davies<sup>2</sup> was able to establish a correlation between bodily habitus, gastric motility and rate of emptying of the gall bladder in normal subjects.

While it has not been proven, it is probable that there are some functions of the normal gall bladder which are influenced by the normal anatomical variations of bodily habitus. A gall bladder with its fundus in the pelvis would be expected to vary in functional activity from one at the costal margin. Some gall bladders lying low in the abdomen, otherwise not remarkable, are said to give rise to clinical symptoms.

Differences in the contraction rates of the human gall bladder in the male and female have been found by Boyden.<sup>3</sup> He found, in 5 out of 7 cases, that the gall bladder in the female, instead of being more sluggish as might have been predicted, empties faster than in the male. The gall bladders of the female were nearly empty in twelve to forty-five minutes after taking a standard meal of egg-yolks and cream, whereas the gall bladders in the males required ninety minutes to respond to the same degree. Boyden was unable to give a satisfactory explanation of the fact that the average emptying time of the gall bladder in young women is quicker than in young men.

In a study of the functional variations of the normal gall bladder, it must be remembered that other organs and systems may influence it. Reach<sup>4</sup> found that the sphincter of the common bile-duct is controlled somewhat by the contents of the stomach. Filling of the stomach caused the sphincter to close and emptying caused it to open. Cole<sup>5</sup> concluded from his experimental work that the tonicity of the sphincter of Oddi is affected by the hydrogen-ion

<sup>1</sup> Mills, R. W.: The Relation of Bodily Habitus to Visceral Form, Position, Tonus and Motility, *Am. Jour. Roentgenol.*, 1917, **4**, 155.

<sup>2</sup> Davies, Francis: Normal Cholecystography, *British Med. Jour.*, June 24, 1927.

<sup>3</sup> Boyden, E. A.: Sex Differences in the Contraction Rate of the Human Gall Bladder, *Proc. Soc. Exper. Biol. and Med.*, 1927, **24**, 353.

<sup>4</sup> Reach, F.: Ueber den Choledochus-Sphinkter, *Arch. Exp. Path. Pharm.*, 1921, **91**, 170.

<sup>5</sup> Cole, W. H.: Relation of Gastric Content to the Physiology of the Common Duct Sphincter, *Am. Jour. Physiol.*, 1925, **72**, 39.

concentration of the gastric content and that the distention of the stomach causes a marked spasm of the sphincter of Oddi.

The observations of Larimore,<sup>1</sup> and of Friedenwald, Feldman and Kearney,<sup>2</sup> indicate that other alimentary factors, such as gastric acidities, peristalsis and secretion, may affect the gall bladder and the production of its shadow. Boyden and Birch,<sup>3</sup> however, find no correlation between the amount of acid in the fasting stomach or the mechanical passage of food through the intestinal tract and the emptying of the gall bladder.

Copher<sup>4</sup> found that the removal of the spleen did not influence the production of a normal cholecystogram. Likewise it was possible to secure normal cholecystograms in animals having an experimentally produced acute appendicitis or an acute general peritonitis. The flow of the pancreatic juice was not found necessary for the normal activity of the gall bladder as indicated by cholecystography. Whitaker has also independently made the latter observation. The rate of secretion of bile by the liver would seem to affect the rate of emptying of the gall bladder somewhat, as has been demonstrated by the choloretic action of neocincophen. Shadows of the gall bladder were found to disappear more rapidly after the administration of this drug. Its action is apparently due to the more rapid secretion of bile rather than stimulation of the gall bladder wall.

The effect of pregnancy upon the emptying of the gall bladder of animals has been studied by Mann and Higgins.<sup>5</sup> They observed that the gall bladder of the pregnant dog, guinea-pig and gopher did not empty or only partially emptied following the ingestion of a fat meal which in non-pregnant animals produced in the same length of time a prompt emptying of the vesicle. The effect of pregnancy on the production of a cholecystogram in 22 women has been made by Crossen and Moore.<sup>6</sup> Three patients in their fortieth week of pregnancy had normal shadows. The remaining patients showed variations from normal, but the authors attributed most of these to roentgenological technical difficulties.

<sup>1</sup> Larimore, J. W.: Cholecystography: Oral Administration of Sodium Tetraiodophenolphthalein, *Radiology*, 1926, **6**, 156.

<sup>2</sup> Friedenwald, J., Feldman, M. and Kearney, F. X.: Experimental Studies in Cholecystography, *Radiology*, 1927, **9**, 68.

<sup>3</sup> Boyden, E. A. and Birch, C. L.: Conditions Affecting the Emptying-time of the Human Gall Bladder, *Proc. Soc. Exper. Biol. and Med.*, 1927, **24**, 827.

<sup>4</sup> Copher, Glover H.: Unpublished work.

<sup>5</sup> Mann, F. C. and Higgins, G. M.: Effect of Pregnancy upon the Emptying of the Gall Bladder, *Proc. Soc. Exper. Biol. and Med.*, 1927, **24**, 930.

<sup>6</sup> Crossen, R. T. and Moore, Sherwood: Application of Cholecystography in Pregnancy, unpublished article.

## PHYSIOLOGICAL CHANGES PRODUCED IN THE GALL BLADDER BY PATHOLOGICAL PROCESSES.

Infection of the gall bladder brings about well-known pathological changes and is probably the greatest etiological factor in the production of cholecystic disease. It seems probable now, however, that pathological changes may take place in the gall bladder which are not primarily of infectious origin. The evidence for this viewpoint will be presented in another chapter and we shall briefly call attention in this section only to some physiological disturbances that result from changes that are ordinarily considered primarily due to infection.

The gall bladder reacts to infection very much like tissue elsewhere in the body. An acute infection causes the usual complicated vascular and cellular response. Though perhaps one or even several acute inflammatory involvements of the gall bladder may resolve without leaving behind a scar, recurrent infection tends to produce a chronic inflammation. Chronic inflammation in the gall bladder is expressed pathologically by increase of connective tissue and accumulation of leukocytes in the wall. There may be areas of peritonitis in the serosa with adhesions to other structures.

Changes in the structure of the gall bladder obviously are likely to produce disturbances of the normal physiology of the organ. The absorptive activity of the gall bladder may be one of the functions disturbed early by the inflammatory reaction. This fact has been proven experimentally and clinically by cholecystography. Active inflammation or its results interfere with the absorptive power of the gall bladder by injuring the lymphatic and blood supply, and consequently they do not permit normal concentration of the iodized phenolphthaleins which are used to produce the shadow after exposure to the roentgen-ray. This interference with concentration expresses itself on the film by a decreased density or by an absence of the shadow of the gall bladder. Clinical application of this fact has been made use of in the diagnosis of various pathological conditions of the gall bladder by the functional test of cholecystography.

The same conclusion, that an inflammatory reaction in the wall of the gall bladder may interfere with absorption, has been arrived at by Bollman, Mann, and De Page<sup>1</sup> after their study of the effect of specific cholecystitis produced by intravenous injections of

<sup>1</sup> Bollman, J. L., Mann, F. C. and De Page, P.: The Effect of Specific Cholecystitis on the Bile-concentrating Activity of the Gall Bladder, *Jour. Lab. and Clin. Med.*, 1925, 10, 544.



sodium hypochlorite, on the bile-concentrating activity of the gall bladder. They found that the time of appearance and rate of development of bile pigment in the blood and urine of animals following ligation of the common bile-duct depended on the degree of involvement of the gall bladder by an experimentally produced acute cholecystitis. Animals having milder degrees of disease of the gall bladder developed jaundice less rapidly than those in which the whole gall bladder seemed diseased. Slight disease caused little or no change in the rate of development of jaundice. These facts, in addition to those obtained by the study of the function of the gall bladder by cholecystograms, indicate that the function of concentration of bile by the gall bladder is impaired or may be totally lost, in the presence of an inflammatory process in the organ.

Active inflammation or its residue also affects the motility of the gall bladder. Shadows of diseased gall bladders were found by cholecystography not to change in size when the pathological changes in the wall were moderately advanced. This fact indicated that the fibro-muscular layer of the wall had lost its distensibility and power of contractility. The observation is of diagnostic value in the determination of whether a gall bladder is normal or pathological. Doubtless too, the malfunctioning of the contractile mechanism prevents normal contraction.

The effect of experimentally produced cholecystitis on the waves of pressure in the gall bladder and common duct was found by Potter and Mann<sup>1</sup> to flatten out the pressure curves and to make them run parallel. This observation indicates that cholecystitis produces profound pressure changes in the biliary tract.

The factors concerned in the accumulation of lipoids in the epithelial cells of the mucosa and later in the connective tissue are not understood. A discussion of this subject will be found in the chapter on The Origin of Gall Stones.

Disease of organs or systems other than the biliary tract may possibly produce changes in the normal physiological activity of the gall bladder, though the organ itself may not be diseased. This is suggested by the findings which have been noted that the gall bladder may be normally influenced by the stomach. Under certain conditions the activities of the normal gall bladder may be influenced by disease of the liver. However, extensive liver damage may not interfere with its normal function. From what

<sup>1</sup> Potter, J. C. and Mann, F. C.: Pressure Changes in the Biliary Tract, *Am. Jour. Med. Sci.*, 1926, **171**, 202.

has been written in other sections of this chapter, it is obvious that pathological conditions of the duodenum or of the common duct sphincter may very well affect the gall bladder.

There is evidence derived from cholecystography that a slightly diseased gall bladder may become practically normal. It is reasonable to believe that the changes that go on in the restitution of parts or healing of wounds may take place in the gall bladder as well as in other parts of the body. The investigations of Reichert<sup>1</sup> have shown that regeneration of lymphatics in the extremities of animals may proceed rapidly after their destruction. Doubtless this is true of veins and blood capillaries. With the restoration of the blood and lymphatic system, it is possible that a healed gall bladder may resume part or all of its normal functions.

#### SECRETION OF SODIUM HYPOCHLORITE AND INTESTINAL TOXINS INTO GALL BLADDER.

An acutely inflamed gall bladder was found by Mann<sup>2</sup> in a high percentage of dogs that had been injected intravenously with a solution of chlorinated soda (Dakin's solution). The reaction follows almost immediately after the injection of 5 to 12 cc. of the solution per kilogram body weight and consists of a breaking down of the capillaries and infiltration of the wall of the gall bladder with blood. The active chemical agent seemed to be chlorin and it reached the gall bladder through the blood stream, producing grossly intense inflammation. Later the entire gall bladder has a tense gangrenous appearance. In some instances the condition became chronic. The production of this chemically induced cholecystitis was not entirely specific since there was often a nephritis and a congestion of the liver produced by the solution.

Copher and Kendall<sup>3</sup> in the course of experimental work relating to intestinal obstruction, found that a cholecystitis is induced by the intravenous injection of material obtained from an obstructed isolated loop of intestine. The reaction was grossly apparent and consisted of edema and cellular infiltration. Other changes, confined principally to the intestines, are produced by the injection of the loop content.

<sup>1</sup> Reichert, F. L.: The Regeneration of the Lymphatics, *Arch. Surg.*, 1926, **13**, 871.

<sup>2</sup> Mann, F. C.: The Production by Chemical Means of a Specific Cholecystitis, *Ann. Surg.*, 1921, **73**, 54.

<sup>3</sup> Copher, Glover H. and Kendall, A. I.: Unpublished work.

**EFFECT OF REMOVAL OF THE GALL BLADDER.**

The effects of removal of the gall bladder on the body economy of the entire organism and on the biliary tract has been noted in thousands of animals and humans. The differences in the biliary tracts between those animals having a gall bladder and those not having it have been studied by Mann, Foster and Brimball.<sup>1</sup> In the preceding sections it has been established that although it is not a vital organ, it is one of considerable importance, particularly for digestion. It has been demonstrated that it serves as a reservoir for the storage of bile secreted by the liver during the periods it is not needed for digestion. A continuous flow of bile from the liver is converted into an intermittent one. The fact that the gall bladder is an expansile chamber makes it possible for it to aid in the regulation of the fluctuating pressures in the biliary tract. Although the capacity of the gall bladder is small compared with the volume of bile secreted by the liver, its storage function is greatly enhanced by its ability to concentrate its content. The full significance of the concentrating activity is probably not known. The discharge of bile into the duodenum by the muscular contraction of the wall of the gall bladder and other forces is efficiently timed to aid in the best manner the digestive processes. The various activities of the gall bladder are closely associated with the activities of the sphincter of the common bile-duct. Animals without gall bladders are said not to have functioning sphincters.

It has been definitely proven by experimental and clinical investigation that cholecystectomy usually produces a dilatation of the bile-ducts. Sweet<sup>2</sup> has found that the small appendages of the bile-ducts, designated as "parietal sacculi" by Beale, because of their analogy to the gall bladder, show hypertrophy after cholecystectomy. If the cystic duct is left *in situ* on removal of the gall bladder, it becomes dilated also. The extent of the dilatation of the ducts from increased intraductal pressure following removal of the gall bladder, is largely dependent on the regulation of the flow of bile into the duodenum by the sphincter of the common duct. Potter and Mann<sup>3</sup> studied the waves of pressure in the common duct after cholecystectomy, and found a marked increase in the amplitude of

<sup>1</sup> Mann, F. C., Foster, J. P. and Brimball, S. D.: Relation of Common Bile-duct to Pancreatic Duct, Jour. Lab. and Clin. Med., 1919-1920, 5, 203.

<sup>2</sup> Sweet, J. E.: The Gall Bladder: Its Past, Present and Future, Int. Clin., 1924, 1, 187.

<sup>3</sup> Potter, J. C. and Mann, F. C.: Pressure Changes in the Biliary Tract, Am. Jour. Med. Sci., 1926, 171, 202.

the rhythmic waves. Judd and Mann<sup>1</sup> found that the ducts failed to dilate after cholecystectomy if the action of the sphincter is obviated. The flow of bile into the duodenum after removal of the gall bladder tends to lose its intermittency and to become continuous, because the increased pressure in the common duct impairs or abolishes the tonicity of the sphincter.

The effect of the removal of the gall bladder on the cholesterol content of the blood of dogs described by Sweet,<sup>2</sup> and the effect on the rate of development of jaundice observed by Mann and Bollman, have been commented on elsewhere.

Although the gall bladder may be removed without noticeably altering the various other organs or metabolic activities of the body, the importance of the physiological functions of the normal gall bladder and its anatomical location stresses the seriousness of the perversion of function of the organ by pathological conditions.

<sup>1</sup> Judd, E. S., and Mann, F. C.: The Effect of Removal of the Gall Bladder: An Experimental Study, *Surg., Gynec. and Obst.*, 1917, **24**, 437.

<sup>2</sup> Sweet, J. E.: The Gall Bladder: Its Past, Present and Future, *Int. Clin.*, 1924, **1**, 187.



## CHAPTER III.

### PATHOLOGY OF CHOLECYSTITIS.

THIS chapter will be devoted only to a consideration of the question of cholecystitis. Gall stones are discussed in the following chapter. In other places, under the appropriate titles, the pathology of the various other conditions of the biliary tract will be discussed together with their clinical features. The term cholecystitis is often loosely used to comprise a number of disturbances of the gall bladder of which some are true inflammations and others are perhaps perversions of the normal functions or of the normal metabolism of the organ. This latter group of cases is often associated with clinical features like those of the less severe cases of the former group, but yet the changes seen on examination of the gall bladder are not those of inflammation in the ordinary sense. Some one has suggested that the inclusive term of "cholecystopathy" might include both groups of cases.

### ETIOLOGY OF CHOLECYSTITIS.

**Incidence.**—Mentzer<sup>1</sup> has published some very interesting data from the Mayo Clinic regarding the incidence of gall bladder disease. In 612 routine postmortem examinations he found pathological evidence of cholecystic disease in 66 per cent of the cases. The large number of people afflicted with gall bladder disease and presenting very few, if any, symptoms can be appreciated by the fact that only 8 per cent of the 612 patients had a primary diagnosis of cholecystitis. The frequency of the disease can be further realized in his statement that 5 per cent of 49,659 new cases at the Mayo Clinic complained of gall bladder trouble. Nine per cent more had gross or microscopic evidence of disease of the gall bladder.

**Sex.**—Gall bladder disease occurs much more frequently in females than in males. The ratio is usually said to be about 2 to 1. In our own series there were about two and a half times as many females as males. But in Blalock's analysis of 888 cases from the Johns Hopkins Hospital the ratio of females to males was 2 to 1.

<sup>1</sup> Mentzer, S. H.: Clinical and Pathological Study of Cholecystitis and Cholelithiasis, Surg., Gynec. and Obst., 1926, **42**, 782.

Pregnancy is an important factor in the production of cholecystitis and particularly of gall stones. A thoroughly satisfactory explanation of this fact has never been presented, but probably of importance in this relationship are the hypercholesterinemia and the biliary stasis in the gall bladder which accompany pregnancy. It is unusual for a woman who has borne four or more children to escape cholecystitis. Osler<sup>1</sup> quotes Naumyn as stating that 90 per cent of women having gall stones have borne children.

**Age.**—The symptoms of gall bladder disease occur most commonly during the fourth decade or later. In Blalock's series most of the cases occurred in the fifth decade. Until recent years cholecystitis in the young was considered to be a rare disease. Although still uncommon, it is our opinion that if cholecystographic examination is carried out more frequently in children many more cases of cholecystitis will be recognized in childhood. We feel also that probably many of the cases first recognized later in life had their origin in childhood, possibly as cases of supposed catarrhal icterus, or of acute indigestion of some sort. In our records at the St. Louis Children's Hospital during the past ten years there were found 8 cases of cholecystitis occurring between the ages of one and a half and fifteen years, practically all of which were confirmed by operation or autopsy. All the cases subjected to operation were found to have large distended gall bladders which were reddened and inflamed but which showed very few adhesions and very little thickening of the wall itself. Snyder<sup>2</sup> states that between the years 1722 and 1922 he found only 80 cases reported of gall bladder disease under the age of ten years. Eusterman<sup>3</sup> has reported 117 cases from the Mayo Clinic, a series which includes males under the age of twenty-five and women under the age of twenty years. These cases represent, however, only 0.85 per cent of the cases of gall bladder disease studied during that period.

**Bacteria.**—Bacteriological investigations of the gall bladder in cases of cholecystitis have been made in two ways, by cultures of the contained bile or other fluid content, and by cultures of the ground-up wall of the organ. Since it is of course the wall that is inflamed it would seem that in the interests of accuracy the procedure of making cultures from the wall, after grinding it, would be the most accepta-

<sup>1</sup> Osler, W.: *The Principles and Practice of Medicine*. 1918, Appleton & Co., p. 569.

<sup>2</sup> Snyder, C. C.: Cholecystitis and Cholelithiasis in Young Children, *Jour. Am. Med. Assn.*, 1925, **85**, 31.

<sup>3</sup> Eusterman, G. B.: Diseases of the Gall Bladder in the Young, *Ann. Clin. Med.*, 1924, **2**, 283.

ble method of bacteriological study, especially since there is no assurance that the bacteria responsible for the disease always gain access to the lumen. Rosenow<sup>1</sup> was probably the first to emphasize strongly the desirability of making cultures from the wall and not merely from the contents of the organ. He studied 47 cases in which the gall bladder was removed at operation, and in many of the cases he made cultures both from the contents and the wall. In many instances cultures obtained from the contents differed from those obtained from the wall, and in some instances cultures from the latter source were positive although the bile was sterile. The prevailing type of organism found in the wall was a streptococcus. Other bacteria which he found in the wall were *Bacillus coli*, *Bacillus welchii*, *staphylococcus*, fusiform and diphtheroid bacilli. In a number of instances also he found living organisms in the centers of gall stones which were different from those in the surrounding bile. This latter finding is in accord with many previous results obtained in the bacteriological examination of calculi. Rosenow's most original contribution is his finding that the streptococci isolated from the wall have an elective localization when injected intravenously into animals. He made the astonishing observation that no less than 79 per cent of the experimental animals developed lesions of the gall bladder, although the next highest percentage of experimental lesions (those in the stomach) was only 29. These findings of Rosenow, and particularly his ideas on elective localization of bacteria, have aroused much discussion and opposition.<sup>2</sup> Brown,<sup>3</sup> however, found streptococci present in 30 per cent of the cases which he studied in which there were slight lesions of the wall and in 75 per cent in which the changes were marked. He thinks that streptococci are the chief etiological factor in cholecystitis and considers that their number is proportionate to the degree of gross and microscopic change.<sup>4</sup> The above findings, probably because they are based on cultures made from the ground-up wall of the gall bladder, differ very materially from most of the bacteriological studies that have been reported, the majority

<sup>1</sup> Rosenow, E. C.: The Etiology of Cholecystitis and Gall Stones and their Production by the Intravenous Injection of Bacteria, *Jour. Infec. Dis.*, 1916, **19**, 527.

<sup>2</sup> See, for example, Holman, W. L.: Focal Infection and Elective Localization, *Arch. Path. and Lab. Med.*, 1928, **5**, 68.

<sup>3</sup> Brown, R. O.: A Study on the Etiology of Cholecystitis and its Production by the Injection of Streptococci, *Arch. Int. Med.*, 1919 **23**, 185.

<sup>4</sup> Illingworth (Types of Gall Bladder Infection: A Study of 100 Operated Cases, *Brit. Jour. Surg.*, 1927, **15**, 221), also, has recently found that streptococci are much more frequently found in the wall of the gall bladder than any other bacteria. He also concludes from his work that infection of the gall bladder seldom occurs through the bile.

of which have been conducted merely on the contents of the organ. Of this latter kind Kelly's<sup>1</sup> studies of Deaver's cases are fairly typical. In 240 cases, *Bacillus coli* was found in 28.33 per cent, *Bacillus typhosus* in 11.25 per cent, *Staphylococcus aureus* in 2.92 per cent, *Streptococcus pyogenes* in 0.42 per cent, *Staphylococcus albus* in 0.83 per cent, *Bacillus coli* and *Staphylococcus aureus* together in 0.83 per cent, unidentified organisms in 2.50 per cent; and the cultures were sterile in 52.92 per cent. In many of the older studies the typhoid and colon bacilli were regarded as being nearly the only organisms present in the gall bladder. The high incidence of sterile cultures made from the bile, and exemplified in Kelly's findings quoted above, is explained by Drennan<sup>2</sup> on the bactericidal action of concentrated bile. Hitherto bile was generally regarded as having little or no bactericidal properties, and the reason for this idea was probably that the experimental studies were made with diluted bile. Johnson,<sup>3</sup> in a measure, has confirmed the finding of Drennan, by obtaining a higher percentage of positive cultures in light-colored (unconcentrated) bile than in the darker concentrated bile. *Bacillus coli* and *staphylococci* predominated in the positive cultures. Judd, Mentzer and Parkhill<sup>4</sup> in 193 cases of diseased gall bladders from which bile was aspirated obtained positive cultures in 28 specimens. But over against this finding were 98 per cent of positive cultures when they were made from the wall of the gall bladder. *Streptococci* and *colon bacilli* predominated in the cultures. For a long time it has been recognized that many cases of cholecystitis have been preceded by *typhoid fever*. A few cases begin during the course of typhoid fever. Blalock found in his series that 28 per cent of all of his cases gave a history of a preceding typhoid infection, an incidence which is considerably higher than that which has been noted in many other series. The cases in Blalock's series which gave the highest incidence of a preceding typhoid were those without stones. The average interval of time which had elapsed between the typhoid fever and the admission to the hospital because of cholecystic symptoms was about five years.

<sup>1</sup> Kelly: Quoted by Stengel, A. and Kern, R. A. in Nelson's Loose-Leaf Living Medicine, vol. 5, p. 505.

<sup>2</sup> Drennan, J. G.: Bacteriological Study of Fluid Contents of One Hundred Gall Bladders Removed at Operation, Ann. Surg., 1922, **76**, 482.

<sup>3</sup> Johnson, W. D.: One Hundred Consecutive Cholecystectomies; Bacteriological and Histological Study of Gall Bladder Lesions, Together with Histological Study of Associated Appendices, Am. Jour. Med. Sci., 1925, **170**, 181.

<sup>4</sup> Judd, E. S., Mentzer, S. H. and Parkhill, E.: A Bacteriological Study of Gall Bladders Removed at Operation, Am. Jour. Med. Sci., 1927, **173**, 16.



**Association with Calculi.**—There has been an extensive controversy for many years concerning the question as to whether the existence of stones in the gall bladder signifies a preceding inflammation of the organ. This question is discussed at some length in Chapter IV. There seems little doubt, however, that in some cases the presence of calculi has preceded a true cholecystitis. In any event there is much evidence that the mechanical and possibly the chemical irritation of the gall stones aggravates an existing cholecystitis.

**Stasis of Bile in the Gall Bladder.**—The importance of biliary stasis in the gall bladder as a factor in the production of cholecystitis has been much discussed. The question is far from settled at the present time. Aschoff and Bacmeister<sup>1</sup> have especially emphasized its importance in the production of biliary calculi. Seelig<sup>2</sup> has recently discussed the possibility of its being a factor in the production of cholecystitis. It is possible that it may have a bearing on the production of some of those disturbances, of which the strawberry gall bladder is an example, conditions in which there seems to be a possible disturbed metabolism of the gall bladder with very little evidence of true inflammation. But on the other hand that type of individual in which stasis is most pronounced on cholecystographic examination, namely, the visceroptotic, is not the type in which biliary disease is most frequent. (See Chapter VII.)

### PATHOGENESIS OF CHOLECYSTITIS.

The most common conceptions of the pathogenesis of infections of the gall bladder and bile tracts are based on four assumed possibilities: (1) Descending infection from the liver by bacteria carried down in the bile; (2) ascending infections from the duodenum up the common bile-duct; (3) hematogenous infections of the gall bladder and ducts; (4) a spreading infection through the wall of the gall bladder from an inflamed contiguous organ. Of these possibilities, it is only the last two which take into serious consideration the actual infection of the deeper layers of the wall of the gall bladder, despite the fact that microscopic examinations of gall bladders removed at operation, at least those which we have studied, demonstrate that there are inflammatory changes not merely in the mucosa but also in the deeper layers and that often these changes are more pronounced in the deeper layers. The other

<sup>1</sup> Aschoff and Bacmeister: *Die Cholelithiasis*, Jena, 1900.

<sup>2</sup> Seelig, M. G.: *Bile-duct Anomaly as Factor in Pathogenesis of Cholecystitis*, Surg., Gynec. and Obst., 1923, **36**, 331.

two possibilities are concerned only with the entrance of organisms into the lumen of the gall bladder, and they do not explain their entrance into its walls. They assume also that contact infection of the mucosa of the gall bladder occurs easily and frequently. But there is no direct evidence to support the idea that cholecystitis occurs, except perhaps occasionally, merely as a result of the entrance of bacteria into the lumen of the gall bladder; and there is much evidence, both clinical and experimental, that such infections are probably rare.

The evidence consists of a number of facts: (1) In experiments performed by one of us (Graham) with Peterman on 10 dogs in which large amounts of pathogenic colon bacilli were injected into the normal gall bladder, no cholecystitis was produced sufficient to be demonstrable by gross appearance or clinical signs, except in one case. In order to produce it with any degree of regularity by the injection of bacteria into the lumen of the gall bladder, it was necessary either to obstruct the outflow from the gall bladder by ligation of the cystic duct or to injure the blood supply by ligation of the cystic artery. In this connection a statement by Meyer, Neilson and Feusier<sup>1</sup> is of interest. These authors state: "It is generally known from the studies of Cushing and from our own, that typhoid bacilli introduced directly into the cystic bile of dogs disappear rapidly and that a cholecystitis can only be produced by considerable injury of the wall, or by placing a foreign body in the gall bladder (Marzer)." (2) Bacteria probably gain access to the gall bladder by being carried down in the bile from the liver in most, if not in all, cases of bacteriemia; yet cholecystitis is comparatively rare in such conditions. Rolleston<sup>2</sup> states that "in typhoid fever the bacilli are always present in the gall bladder, but cholecystitis is comparatively infrequent." Osler<sup>3</sup> states that cholecystitis occurred in only 19 of his series of 1500 cases. (3) Theoretically, the mere presence of bacteria within the lumen of the gall bladder should be of no more significance in producing cholecystitis than that the presence of bacteria in the urine should imply an inflammation of the urinary bladder. It is well known that bacteria are frequently passed in the urine in large amounts without the coincidence of cystitis, especially in typhoid fever.

If the assumption is correct that the wall of the gall bladder

<sup>1</sup> Meyer, K. F., Neilson, N. M. and Feusier, M. L.: *The Mechanism of Gall Bladder Infections in Laboratory Animals*, Jour. Infec. Dis., 1921, **28**, 456.

<sup>2</sup> Rolleston, H. D.: *Diseases of the Liver, Gall Bladder and Bile-ducts*, New York, the Macmillan Company, 1912, p. 608.

<sup>3</sup> Osler, William: *Practice of Medicine*, 1905, p. 83,

beneath the mucosa is involved in most cases of cholecystitis, then it would seem reasonable to discard the idea of the serious importance of contact infections of the mucosa by organisms within the bile, particularly in view of the evidence outlined above. How then may an infection originate in the wall? It is obvious that in general only two routes are available for the transmission of organisms to the wall. One of these is the blood stream and the other is the lymph stream.

In 1909, Koch<sup>1</sup> demonstrated clumps of bacilli in the wall of a gall bladder and concluded that typhoidal cholecystitis is due to capillary embolism. In the same year, also, Chiarolanza,<sup>2</sup> working under Koch's direction, came to the same conclusion. Rosenow<sup>3</sup> has particularly emphasized the idea of the hematogenous origin of cholecystitis. Meyer<sup>4</sup> and his collaborators, in their exhaustive article on the mechanism of gall bladder infections, report experiments on 500 rabbits in which they attempted to produce a condition analogous to the human typhoid carrier state. They consider that the findings of Koch and Chiarolanza of bacterial emboli in the wall of the gall bladder during typhoid to be "exceptionally rare" and concerned with an "exceedingly severe and unique form of typhoid cholecystitis." They arrive at this conclusion partly because in their own experiments, even after the intravenous injection of enormous doses of typhoid bacilli (8000 to 24,000 million), only about one-third of the rabbits presented histological evidence of an infection through the terminal capillaries of the mucosa, and also because, as they state, examination of human gall bladders in cases of death from typhoid shows a capillary embolism only occasionally. They are inclined, however, to consider very seriously, especially in the rabbit, the possibility of contact infection of the mucosa of the gall bladder by bacteria carried down in the bile from the liver, and they hold the opinion that deep infections of the wall are frequently the result of a spread of the infection from the mucosa. In human typhoid carriers, they consider that "the embolic infection of the gall bladder wall plays an insignificant rôle." They state, furthermore, that "a condition analogous to that found in man apparently exists in the guinea-pig. The microscopic

<sup>1</sup> Koch, J.: Typhusbazillen und Gallenblase, *Ztschr. f. Hyg. u. Infektionskrankh.*, 1909, vol. 62, pt. 1.

<sup>2</sup> Chiarolanza: Experimentelle Untersuchungen ueber die Beziehungen der Typhusbazillen zu der Gallenblase und der Gallenwegen, *Ztschr. f. Hyg. u. Infektionskrankh.*, 1909, 62, 12.

<sup>3</sup> Rosenow, E. C.: The Etiology of Cholecystitis and Gall Stones and their Production by the Intravenous Injection of Bacteria, *Jour. Infec. Dis.*, 1916, 19, 527.

<sup>4</sup> Meyer, K. F., Neilson, N. M., and Feusier, M. L.: *Loc. cit.*

and cultural study of a limited number of gall bladders derived from infected guinea-pigs convinces us that the wall is rarely, and then only slightly, infected through the bile." This then seems to constitute another argument against the frequency of contact infection of the gall bladder in man. There can be little doubt apparently that cholecystitis not infrequently is hematogenous in origin; but yet we do not believe that an explanation based on this idea is sufficient for most cases of spontaneous cholecystitis, especially those which are not typhoidal in origin. The well-known, striking tendency of cholecystitis to be associated with appendicitis and other inflammatory lesions of the portal system must be something more than a coincidence. Birch-Hirschfeld,<sup>1</sup> in 1895, considered that organisms were carried to the liver and from there to the gall bladder by the bile. Since then, the "hematohepatogenous" idea of the origin of cholecystitis has been a popular one. But, as we have already shown, the idea of a contact infection of the mucosa of the gall bladder has very little to support it, at least so far as its being a frequent occurrence in man. Furthermore, it is difficult to explain the association of appendicitis and other portal infections with cholecystitis on the basis of a hematogenous infection of the wall of the gall bladder, because there is no direct path from the appendix to the gall bladder by way of the blood stream. The entire arterial supply of the gall bladder comes from the hepatic artery. The cystic artery supplies most of the blood; but there are in addition a few small branches of the hepatic artery which reach the gall bladder through its attachment to the liver. The veins of the gall bladder all empty into the portal vein. If organisms, therefore, are to be carried from the appendix to the gall bladder by the blood stream, they must either travel through the whole systemic circulation back through the hepatic artery to the gall bladder or there must be a retrograde passage of them from the liver into the gall bladder through the tributaries of the portal vein. If the first alternative were correct, then there would be no more reason for cholecystitis to be associated with appendicitis than with infections elsewhere in the body, as the hand for example. The second alternative is based on the slender support of a comparatively rare possibility, a retrograde thrombosis, or at least a retrograde pyelephlebitis.

There is, however, one route between the appendix and gall bladder which is comparatively direct and easy to understand, and

<sup>1</sup> Birch-Hirschfeld: Quoted by Meyer, K. F., Neilson, N. M., and Feusier, M. L.: *Loc. cit.*



that is a "hematolymphatic" route. Sudler<sup>1</sup> has shown a very intimate lymphatic connection between the liver and gall bladder through the attachment of the gall bladder to the liver. This is shown in Figs. 13 and 14, pages 31 and 32. We have repeated some of Sudler's experiments and have confirmed his idea of the general arrangement and anastomosis of the hepatic and cholecystic lymphatics. The lymph vessels of the gall bladder may be seen after

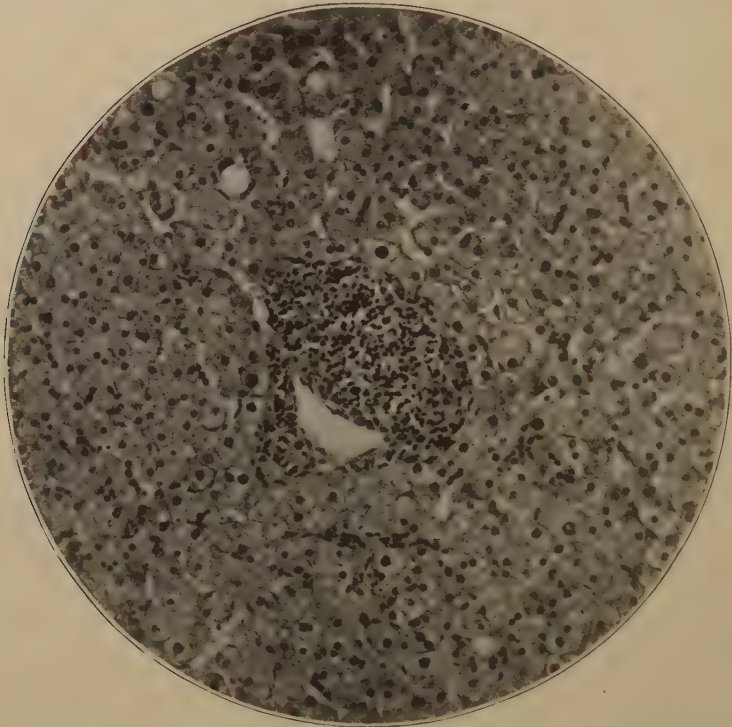
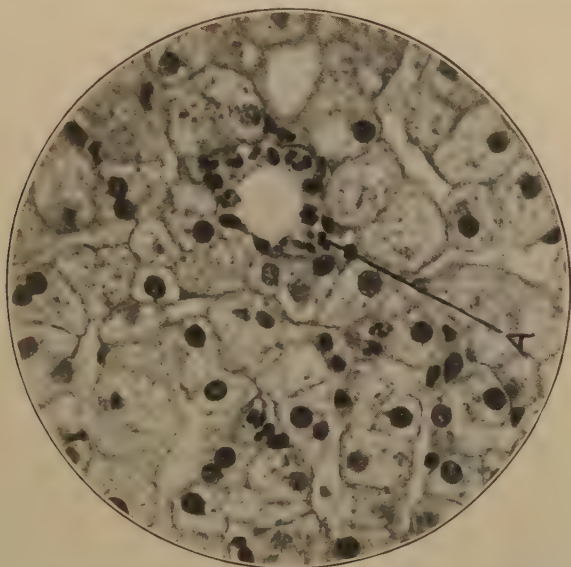


FIG. 65.—A common type of hepatitis occurring in association with a subacute cholecystitis. The periportal sheaths are densely infiltrated with leukocytes, chiefly of the polymorphonuclear variety. From a study of small pieces of liver removed at operation in cases of cholecystitis, either with or without stones, it has been noted that some degree of hepatitis is a constant accompaniment of cholecystitis.

injections of such a substance as Prussian blue into the portal vein. Conversely, also, injections made into the wall of the gall bladder not only follow the lymphatics into the liver in the interlobular sheaths but also may be seen to pass along the lymphatics of the common duct. An infection of the liver, therefore, would tend to

<sup>1</sup> Sudler: The Architecture of the Gall Bladder, Bull. Johns Hopkins Hosp., 1901, 12, 126.

spread to the gall bladder by way of the lymphatics, and conversely an infection of the gall bladder would tend to spread not only to the liver but also along the common duct. In this respect, infections in this region would merely follow the rule of infections elsewhere in the body. We should expect to find evidence, therefore, that in cases of cholecystitis there is also an associated inflammation in the liver.



<sup>1</sup> FIG. 66.—Higher-power magnification of another part of the same liver, showing accumulation of polymorphonuclear leukocytes around a small bile-duct, indicated by line marked A.

In 1918, one of us<sup>1</sup> showed in a series of cases in which small pieces of the liver were removed at operation for cholecystitis that microscopic evidence of hepatitis existed in every case. The inflammation was chiefly in the interlobular sheaths and appeared to be a pericholangitis. (Figs. 65, 66 and 67.) This location of inflammatory changes is in harmony with the idea of a lymphangitis, for it is here that the hepatic lymph vessels are chiefly situated.<sup>2</sup> In another paper,<sup>3</sup> we showed that in the dog experimental cho-

<sup>1</sup> Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, *Surg., Gynec. and Obst.*, 1918, **26**, 521.

<sup>2</sup> Mall, F. P.: On the Origin of the Lymphatics in the Liver, *Bull. Johns Hopkins Hosp.*, 1901, **12**, 146.

<sup>3</sup> Peterman, M. G., Priest, W. S., Jr. and Graham, E. A.: The Association of Hepatitis with Experimental Cholecystitis and its Bearing on the Pathogenesis of Cholecystitis in the Human, *Arch. Surg.*, 1921, **2**, 92.

lecystitis is constantly accompanied by a hepatitis of the same sort as already observed in man. It is interesting that when this occurs secondarily to the production of a cholecystitis the right lobe of the liver is very much more affected than the left lobe, and the most marked changes of all are in the right lobe near the gall bladder. This all seems to indicate that the spread of the infection



FIG. 67.—Chronic hepatitis (biliary cirrhosis) in a woman who had a history of gall bladder trouble extending over a period of fifteen years. Jaundice had never been present; therefore, there had been at least no marked biliary obstruction. At operation stones were found in the gall bladder. The marked thickening of the small ducts is strikingly evident.

to the liver from an already inflamed gall bladder must occur through the lymphatics rather than through the veins, because in the latter instance, since the veins are tributaries of the portal vein, a more even distribution of the infection through the liver would be expected. The possibility of the establishment of a vicious circle between an infected gall bladder and the liver, whereby each may reinfect the other through the lymphatics, becomes readily apparent. This



finding of the constancy of a hepatitis in association with cholecystitis has been confirmed by Judd,<sup>1</sup> who states, "A review of our studies inclines us to believe that cholecystitis rarely exists without hepatitis." In our original paper, to which reference has already been made, it was said that in a series of thirty consecutive cases coming to operation for gall bladder disease an enlargement of the liver was noted in 87 per cent. Subsequent observations have not

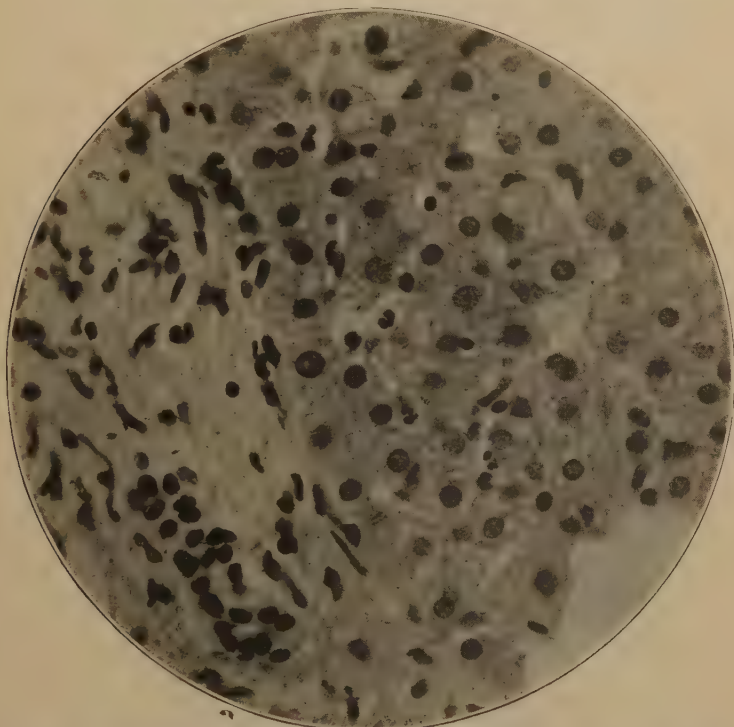


FIG. 68.—Hepatitis in association with chronic appendicitis; piece of liver removed at operation for chronic appendicitis; no evidence of cholecystitis. Note polymorphonuclears in lobule near its periphery.

borne out this high percentage, and we are forced to the conclusion that the actual percentage of noticeable enlargement of the liver is very much smaller than the figure given.

If we are to explain the frequent association of appendicitis with cholecystitis on the basis of a primary infection of the liver from the appendix by way of the portal vein, and of a cholecystitis resulting

<sup>1</sup> Judd, E. S.: Relation of the Liver and Pancreas to Infection of the Gall Bladder, *Jour. Am. Med. Assn.*, 1921, **77**, 197.



from that secondarily, by way of a lymphatic spread from the liver to the gall bladder, then obviously it would seem necessary to find evidence of hepatitis in association with appendicitis. In a few cases which came to operation for chronic appendicitis, we removed small pieces of the liver for examination. (Figs. 68 and 69.) In three cases there were definite areas of infiltration in the liver (both polymorphonuclears and round cells). In none of those cases was there any evidence, either clinical or at operation, of cholecystitis.

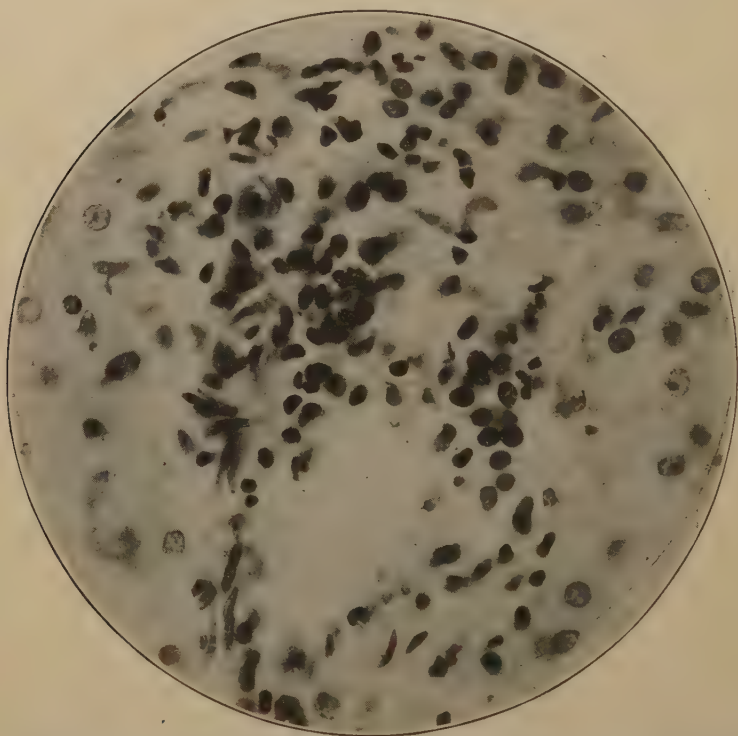


FIG. 69.—Hepatitis with chronic appendicitis, showing leukocytic infiltration in interlobular tissue; piece of liver removed in another case of chronic appendicitis; no evidence of cholecystitis.

This fact seems important since in consequence the existing hepatitis could hardly be assumed to have been secondary to a cholecystitis. We have frequently noted slight liver tenderness in association with chronic appendicitis and have considered the sign of some importance in diagnosis. The question may arise as to why cholecystitis did not occur in the cases of hepatitis with appendicitis illustrated here. The answer is, of course, difficult, but perhaps the intensity of the hepatitis was not sufficient.

It is interesting that even those who favor the idea of the contact infection of the mucosa of the gall bladder by bacteria carried in the bile from the liver, the so-called "hematohepatogenous" theory, are forced to assume some degree of inflammation of the liver preceding the infection of the gall bladder. This question is discussed at some length by Meyer and his collaborators who state that "dosage, virulence and *lesions* (italics ours), and not the secretory, detoxifying activity of the liver, are the prerequisites for the passage of bacteria from the blood to the bile capillaries. . . . The conception of a purely mechanical passage deserves little consideration."

Wyssokowitch<sup>1</sup> and also Blachstein<sup>2</sup> considered liver necroses prerequisites for the infection of the biliary passages in typhoid. If it is granted then that some degree of inflammation of the liver must be present before the bile can be infected, it seems only reasonable to assume that in many cases the infection will spread by means of the lymphatics and will therefore involve the gall bladder wall. Meyer states that "from an experimental standpoint the lymphatic route is of no importance," but yet he says that "in the course of peritonitis or other abdominal infections (appendicitis), streptococci can be transported through the lymphatics to the biliary passages," and again, "the so-called ascending route of infection is in all probability due to an invasion of bacteria through the lymphatics." He also states that in about 1 per cent of the rabbits and guinea-pigs used there was a spontaneous cholecystitis due to *Bacillus coli*, streptococci or staphylococci. In these cases, "occasionally the bile appeared to be normal while the histological picture exhibited a low-grade infection of the lymphatics of the mucosa and subserosa."

We believe that there is some confusion about what is meant by the biliary lymphatics. Meyer and his collaborators speak of them as if they were entirely extra-hepatic, and apparently they do not recognize that the extra-hepatic lymphatics are continuous with those within the liver. This is the common conception of the lymphatics of the biliary tract. Sudler's important work is too little known. As a matter of fact, we do not see why nearly all the results on experimental cholecystitis cannot be just as easily interpreted on the basis of a lymphatic infection of the wall as on the idea either that there has been a contact infection of the mucosa

<sup>1</sup> Wyssokowitch: Quoted by Meyer, K. F., Neilson, N. M. and Feusier, M. L.: Loc. cit.

<sup>2</sup> Blachstein: Quoted by Meyer, K. F., Neilson, N. M. and Feusier, M. L.: Loc. cit.

or an infection of the wall directly through the blood stream. We admit, however, the possibility of infection through both of the latter means; but we are inclined to believe that the idea of a lymphatic origin secondary to a hepatitis explains many of the cases of cholecystitis in man better than any other.

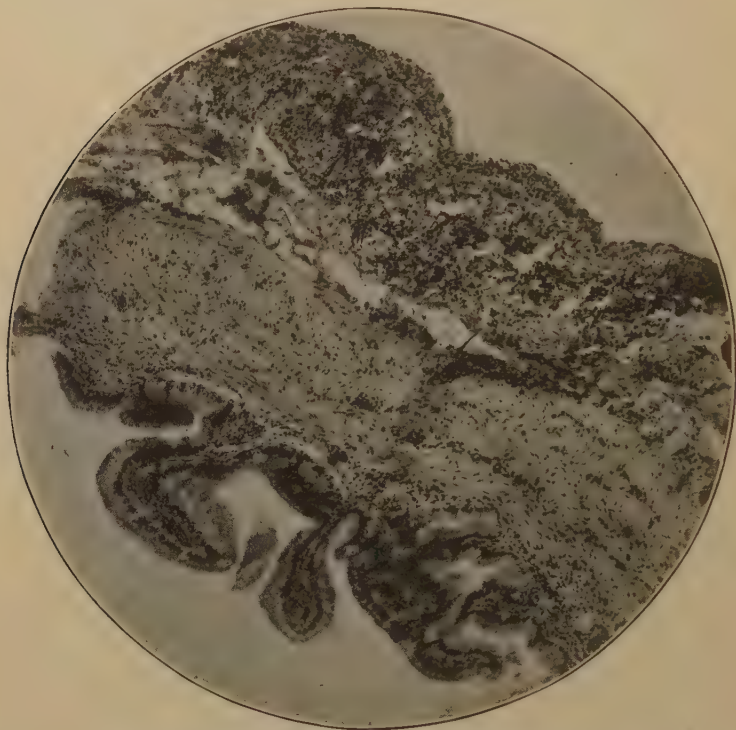


FIG. 70.—Experimental cholecystitis from Dog 1 by injection of portal vein; extensive inflammation of wall; mucosa relatively unaffected.

In animal experiments, we have obtained results which we believe tend to support the idea of the lymphatic origin not only of cholecystitis but also of inflammation of the common duct. These experiments have consisted of several types. Two types are of particular interest here because of their special bearing on the idea of the lymphatic origin of cholecystitis and its complications. One of these groups of experiments has already been referred to above. It consisted in the production of hepatitis secondary to experimental cholecystitis, induced by direct inoculation of rather large amounts of organisms into the lumen of the gall bladder after ligation of the

cystic duct and artery. The hepatitis produced conformed to that which had already been seen in cases of cholecystitis in man, and for the reasons given above, it was considered as most probably representing a lymphatic spread to the liver. The other type of experiment consisted in the production of hepatitis, cholecystitis, and choledochitis by portal vein injections. It was felt that if cholecystitis and its common complications could be interpreted

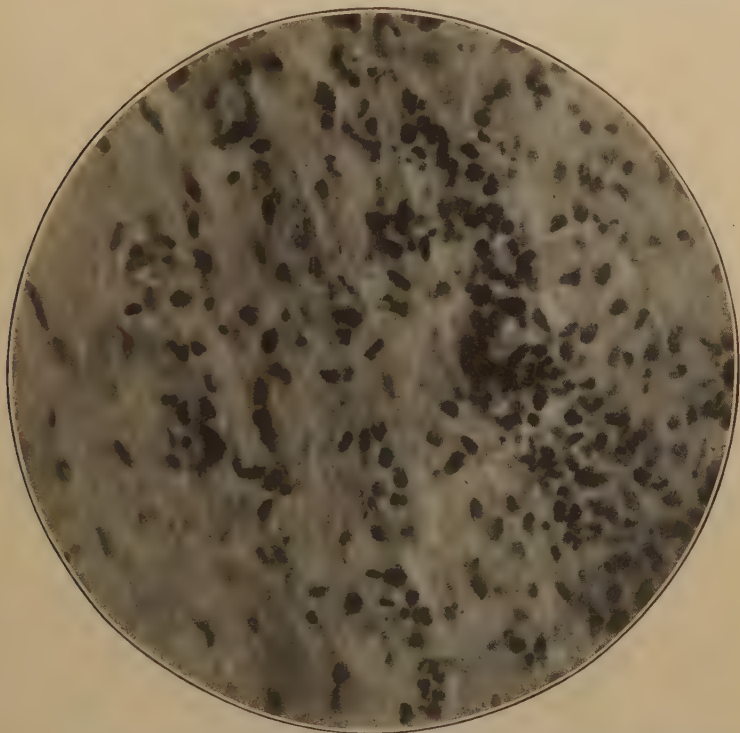


FIG. 71.—Higher power photomicrograph of specimen shown in Fig. 70, showing leukocytic infiltration of wall of gall bladder.

on the basis of a lymphatic spread from a liver in which the periportal spaces were the seats of inflammation, then it should be possible often in a single experiment to produce by injection of the portal vein a simultaneous hepatitis, cholecystitis and choledochitis. Not only was it possible to do this repeatedly, but the types of lesion found agreed with those which occur in spontaneous cases in man. (Figs. 70, 71 and 72.) It was possible also after the injections to demonstrate the infecting organisms in the liver, in



the wall of the gall bladder and in the wall of the common duct. The same results occurred regardless of whether the injections were made into the main trunk of the portal vein or into one of its radicles, as the appendix vein. We believe, therefore, that the results obtained are comparable to the cases of cholecystitis in man which may be considered as following appendicitis or some other lesion of the portal system. For a detailed account of the experiments see the article by Graham and Peterman.<sup>1</sup>

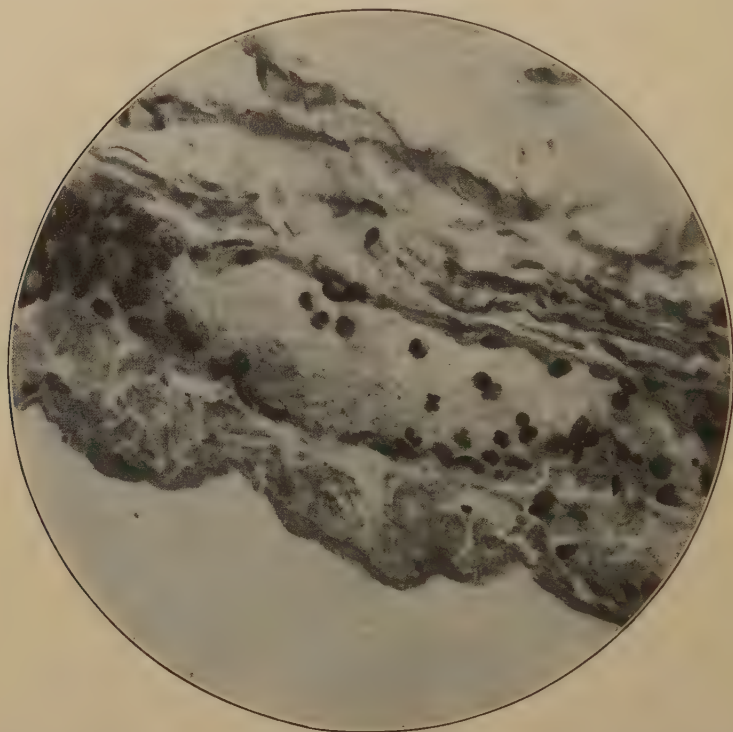


FIG. 72.—Experimental cholecystitis. This shows apparently a lymphatic vessel in the outer layer of the gall bladder containing polymorphonuclear leukocytes and presenting other evidence of acute inflammation.

We feel, therefore, that in many cases, perhaps in a majority, cholecystitis represents a direct extension to the wall of the gall bladder from a liver already inflamed. The hepatitis usually begins and is most marked in the interlobular, or periportal, tissues,

<sup>1</sup> Graham, E. A., and Peterman, M. G.: Further Observations on the Lymphatic Origin of Cholecystitis, Choledochitis and the Associated Pancreatitis, *Arch. Surg.*, 1922, 4, 23.

and it is apparently due to infection brought to the liver by the portal vein, and, more rarely perhaps, by the hepatic artery. A pericholangitis then occurs, and because of the intimate anastomosis between the lymphatics of the intra-hepatic and extra-hepatic biliary systems a direct extension into the wall of the gall bladder takes place as well as into the common duct. From the antecedent hepatitis, therefore, a cholecystitis, and choledochitis can be understood to occur if in the consideration of inflammations in this locality we apply the well-known fact concerning inflammation in general, namely, that it extends by way of the lymphatics. We believe that these ideas explain more readily than any others heretofore offered the frequent and well-recognized association of biliary tract infections with lesions of the portal system (appendicitis, peptic ulcer, typhoid fever, etc.). Hepatitis also follows the experimental production of cholecystitis by direct inoculation of organisms into the gall bladder. This fact suggests that, frequently perhaps, a vicious circle between the gall bladder and liver is established whereby each may reinfect the other. Removal of the gall bladder would probably break the circle. The ideas here expressed also furnish added evidence of the necessity of treating, in addition to the gall bladder, any coëxisting lesions of the portal system.

While the opinion is expressed here that many cases of cholecystitis represent a lymphatic spread from the liver, we recognize also that some are doubtless hematogenous in origin, some perhaps are contact infections from bacteria carried down in the bile and a few perhaps may have originated in an ascending infection of the common duct through its lymphatics or have been due to a chance contact of a gall bladder with an inflamed contiguous organ.

George Müller<sup>1</sup> as early as 1904 suggested the lymphatic origin of cholecystitis. He apparently, however, considered it as of rather rare occurrence. Heyd, Killian and MacNeal<sup>2</sup> have reinvestigated this whole question. By using the same method of examining the liver as we had used in our earlier work, namely, the removal of a small piece for histological study, they came to conclusions which closely agreed with ours which have already been mentioned. For example, they found that severe inflammation in the region of portal drainage frequently is associated with inflammation in the liver which leads to fibrous thickening of the trabeculae of Glisson's capsule; such primary inflammation is most common in the appendix

<sup>1</sup> Müller, G.: *Pathology of Cholecystitis*, Brooklyn, Med. Jour., 1905, **19**, 11.

<sup>2</sup> Heyd, C. G., Killian, J. A. and MacNeal, W. J.: *The Liver and its Relation to Chronic Abdominal Infection*, Beaumont Lectures, 1924, C. V. Mosby Company, St. Louis.

but may occur in other organs. They concluded also that the inflammation may frequently extend from the liver to the gall bladder, either through the bile or through the lymphatic channels, and the cholecystitis thus initiated may subsequently, in its repeated exacerbations, bring about localized or even general hepatitis by lymphatic extension of the infectious process. Martin,<sup>1</sup> however, in his recent Mütter lecture directs a considerable amount of criticism against our ideas of the pathogenesis of cholecystitis by a lymphatic spread from the liver. It is a little difficult to follow his argument, but apparently his objection is very largely a quantitative one, as if we had concluded that all cases of cholecystitis arise by a lymphatic spread from the liver since he states that "one would expect that occasionally bacteria would be carried by the lymph stream to the wall, but it is difficult not to believe that the thousands of organisms in the infected bile must play a most important part in producing lesions of the gall bladder." Of course we have never claimed that all cases of cholecystitis were produced by the lymphatic route. He evidently merely differs from us, therefore, in the relative frequency of such an occurrence. It is obviously impossible at the present time to state how often such a course of events may happen. We are inclined to think that it is a fairly frequent occurrence. In any case, however, the possibility of a lymphatic origin of cholecystitis seems to have been utterly neglected hitherto. We offered the idea as an additional one to those ideas already existent. In view of the abundant lymphatic anastomosis which exists between the liver and the gall bladder it would seem reasonable to expect that infection might pass from one organ to the other, unless infections of these organs fail to follow the custom of infections in other parts of the body in which it is notorious that they pass through the lymph channels. Martin does not dispute this abundant lymphatic connection nor does he present any convincing evidence that biliary tract infections are unique in the fact that they do not spread through the regional lymphatic vessels. It seems quite out of place to enter into a detailed rebuttal here of his paper. We feel impelled, however, to call attention particularly to the new evidence presented in Chapter VIII that, as shown by tests of the liver to excrete the dye, phenol-tetraiodophthalein, there is usually definitely impaired function in cases of cholecystitis and also of appendicitis. These results would harmonize with our ideas of a frequent hepatitis coëxisting with the

<sup>1</sup> Martin W.: Hepatitis and its Relation to Cholecystitis, *Ann. Surg.*, 1927, **85** 535.

conditions named, ideas which Martin apparently is unwilling to accept.<sup>1</sup>

Mention should be made also of the interesting experimental cholecystitis produced in dogs by Mann<sup>2</sup> by the intravenous injection of Dakin's solution of sodium hypochlorite. An intense congestion with hemorrhages followed in many instances, and in some cases actual necrosis occurred.

### VARIETIES OF CHOLECYSTITIS.

There is nothing specific about the pathological changes in the gall bladder in cases of ordinary inflammation.

**Acute Cholecystitis.**—Acute cholecystitis reveals itself in many forms. In the simplest forms the organ is often reddened, the wall is somewhat thickened and edematous, and the mucous membrane, in addition to being reddened and congested, may show more than the normal amount of mucus upon it. From this stage it may pass into a suppurative form. In the latter condition, which is often called *empyema of the gall bladder*, the organ usually appears greatly swollen and tense. It may show various shades of red and brown in color, and in cases of gangrene it may be black in places. Usually, there are also patches of fibrin deposited on the external surface which are cream-colored or yellowish, gray. In such a condition the gall bladder is most frequently adherent to other viscera by thick fibrinous adhesions and it may be partially covered by the omentum. Cases of suppurative cholecystitis are nearly always associated with an obstruction of the cystic duct, which is most often caused by a stone impacted in the duct. The contents of the organ are pus, which may or may not be bile-stained, depending very largely upon the duration of the acute suppuration. The pigment of the contained bile usually disappears within a few days in the presence of the pus in the gall bladder; but if the case is of more recent origin the contents are likely to be brownish with a thick sediment of pus and sometimes with blood. Other stones than the one causing the obstruction of the duct are usually present in the gall bladder. The regional lymphatic glands are enlarged and sometimes contain pus. Perforation of the organ may occur, but

<sup>1</sup> In a recent article Moynihan (*The Gall Bladder and Its Infections*, Brit. Med. Jour., 1928, 1, 1) states that he has abundantly confirmed our finding that hepatitis, if not an invariable, is at least a very frequent accompaniment of cholecystitis. He has also found that the outer coats of the gall bladder in a large proportion of cases are more extensively affected than the inner.

<sup>2</sup> Mann, F. C.: *The Production by Chemical Means of a Specific Cholecystitis*, Ann. Surg., 1921, 73, 54.



fortunately this accident is rare. There is, however, a fairly high incidence of perforation in the cases of acute cholecystitis which occur during the course of typhoid fever. Armstrong<sup>1</sup> stated that in 2051 cases of typhoid treated at the Montreal General Hospital from 1897 to 1910 there were 93 cases of perforation of the gall bladder, an incidence of 4.53 per cent. In addition he had seen 4 other cases. Of the 97 perforations, 78 were operated upon and 24 recovered. Camac<sup>2</sup> found even a higher incidence of perforation in his series. In 115 collected cases of acute cholecystitis occurring during the course of typhoid fever he found 21 perforations of the gall bladder, an incidence of 18 per cent. The perforation does not always lead to a general peritonitis because often its site is walled off by adherent viscera. The perforations which occur in typhoid fever differ from those which occur in *empyema* of the gall bladder in the fact that usually there is no obstruction of the cystic duct and no gall stones present in the former.

Microscopic examination of the gall bladder in cases of acute cholecystitis shows usually the whole wall invaded by leukocytes and areas of hemorrhage are common. In many cases the deeper layers, especially the subserous layer next to the peritoneum, are the sites of the most severe inflammatory changes. But in some cases, particularly those in which stones are present, the mucous membrane shows more signs of inflammation than the deeper layers of the wall. In the more severe grades the epithelium may be destroyed in places, but it is a striking fact that it rarely, if ever, is completely destroyed by inflammation. (Fig. 73.) In our own experience we have never seen complete loss of epithelium as a result of inflammation. This experience seems to agree also with that of Boyd<sup>3</sup> who states that "it is remarkable how intact the epithelium may be in the worst looking gall bladders." We feel also that this demonstrated resistance of the epithelium to even the most severe grades of inflammation is another argument against the idea of the frequency of a purely contact infection of the mucosa as a mode of origin of cholecystitis. In the light of this fact it is hard to reconcile with the experiences of others the findings of Chandler<sup>4</sup> and Newell who in a recent article found the mucosal

<sup>1</sup> Armstrong, G. E.: Typhoid Perforations and Perforations of the Gall Bladder, British Med. Jour., 1910, ii, 1298.

<sup>2</sup> Camac: Studies in Typhoid Fever, Series III, Johns Hopkins Hosp. Rep., vol. 8.

<sup>3</sup> Boyd, W.: Surgical Pathology, 1925, W. B. Saunders Company, Philadelphia, p. 349.

<sup>4</sup> Chandler, L. R. and Newell, R. R.: Cholecystography and Pathological Changes in Gall Bladder; Correlation as Observed in 50 Consecutive Cases, Jour. Am. Med. Assn., 1927, 88, 1550.

epithelium entirely gone in a large proportion of gall bladders removed at operation, even although many were said to have been normal by cholecystographic examination. We suspect that too long an interval of time had been allowed to elapse between the removal and the fixation of the organs. It is well known that *postmortem* the epithelium of the gall bladder disappears in about five or six hours. To get the best results in the microscopic examination of a gall bladder, the whole organ should be filled with the

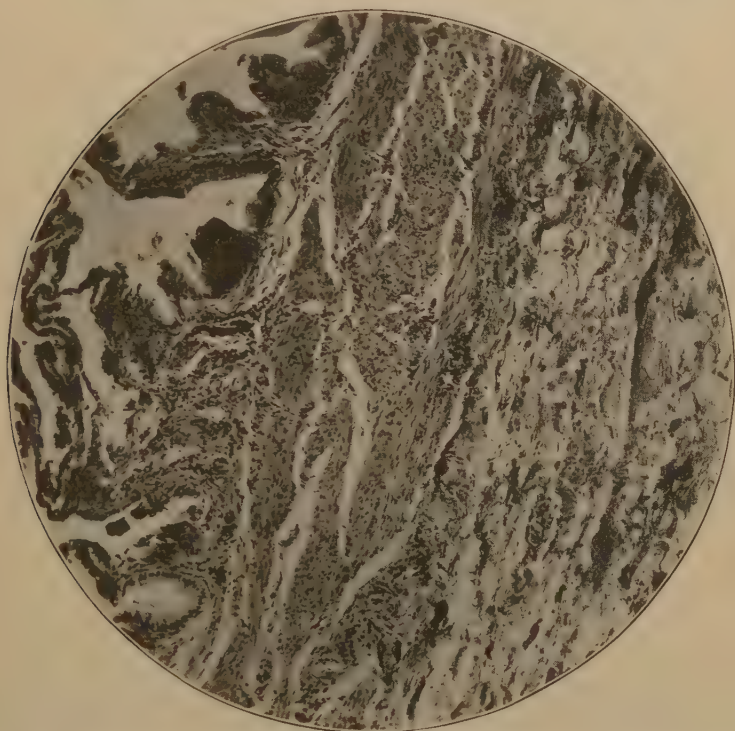


FIG. 73.—Cholecystitis with stones; whole wall, including mucosa, markedly inflamed.

fixing fluid after removal of its contents and it should then be also completely immersed in the fluid. Pieces should be removed from the wall after the fixation has been completed. If they are removed before fixation the whole mucosa is likely to retract away, and unless unusual care is exercised in the cutting of the sections it will seem as if no mucosa is present.

It is our belief that in general too much attention is devoted by pathologists to the examination of the mucosa and not enough to the

examination of the deeper layers of the wall. It is important to have more information concerning the deeper layers in cases of cholecystitis because in that way it will be more easily determined whether the infection usually begins in the mucosa or in the deeper layers. It is possible of course for the infection in the mucosa to spread to the deeper parts of the wall and *vice versa* by means of

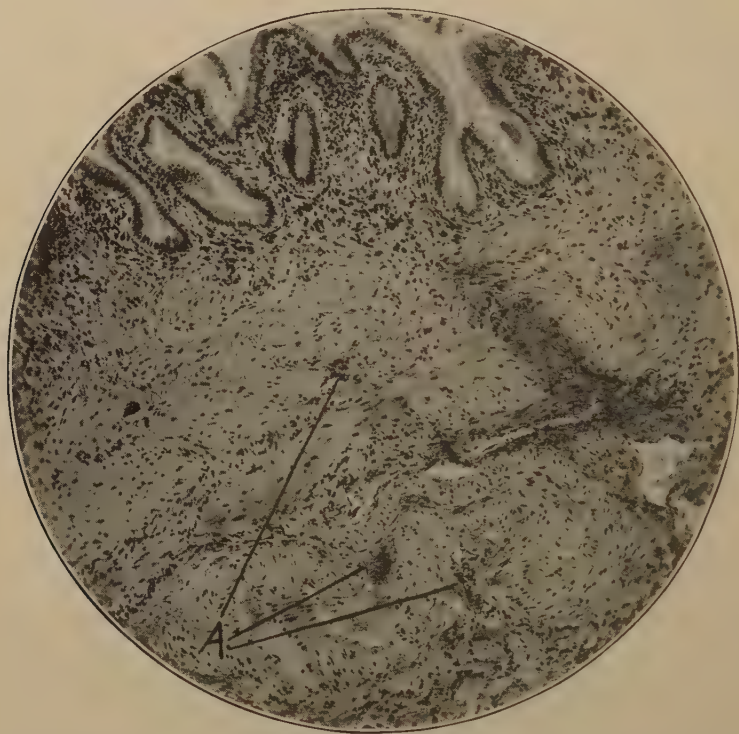


FIG. 74.—Gall bladder removed at operation in case of cholecystitis without stones. Deep in the fibro-muscular layers at a considerable distance from the mucosa were found collections of polymorphonuclear leukocytes, designated by lines marked A. These are usually much more conspicuous in the deeper layers than in the mucosa. Normally, the mucosa contains large numbers of round cells (lymphocytes).

lymphatic vessels which pass through the layers of the wall. The finding of greater or less degrees of inflammation in particular depths of the wall will therefore not constitute absolute proof of whether in a particular case of cholecystitis the infection has started in the mucous membrane or in the lymphatic vessels at the periphery of the gall bladder. But at least the knowledge that in the majority of cases the preponderance of inflammation is at one site or the other

would be suggestive evidence as to whether the infection usually begins in the mucosa or in the subserous lymphatic vessels. (Figs. 74, 75, 76, 77 and 78.)

**Chronic Cholecystitis.**—Acute inflammations of the gall bladder very often pass into a chronic stage. Clinical observation over a long period of time has revealed the fact that apparently in the great majority of cases a gall bladder that has once become infected

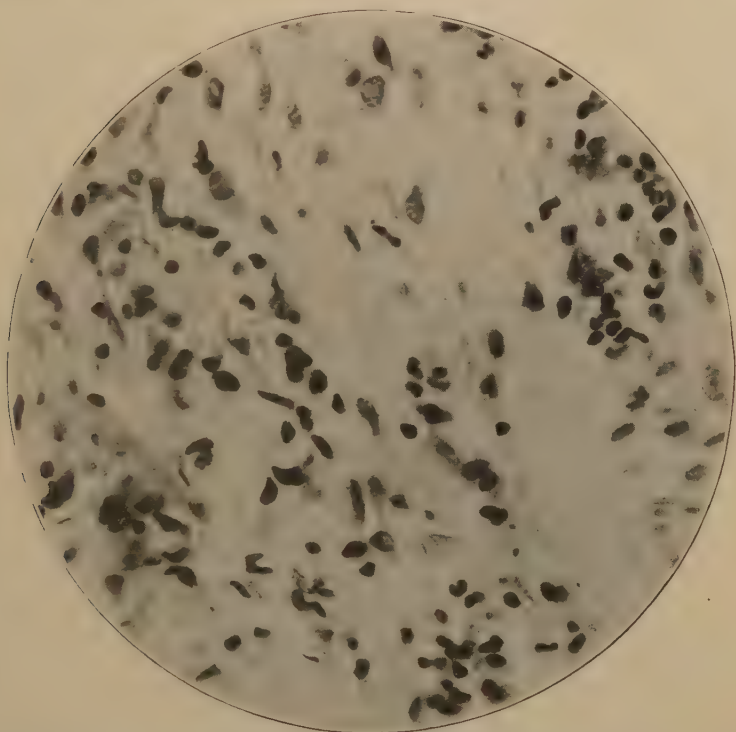


FIG. 75.—Higher magnification of same gall bladder as shown in Fig. 74. The leukocytic infiltration shown here is deep in the wall of the gall bladder at a considerable distance from the mucosa.

remains so. On the other hand there seem to be cases in which complete recovery occurs after a single attack of acute cholecystitis. It is not clear at the present time why there is so little tendency for infections of the gall bladder to become healed spontaneously. Many cases of chronic cholecystitis begin insidiously without a preceding attack of acute inflammation. There are again other cases which are commonly designated as chronic cholecystitis but which really present only slight anatomical evidence of inflammation. It is



is probable that many of these latter cases are really expressions of an abnormal metabolism rather than of a true inflammation of the gall bladder.

In chronic cholecystitis the gall bladder is thickened, and its color is grayish because of the presence of fibrous tissue. (Fig. 79.) In advanced cases the thickening is sometimes so great that the diameter of the wall attains a thickness of a centimeter or more.

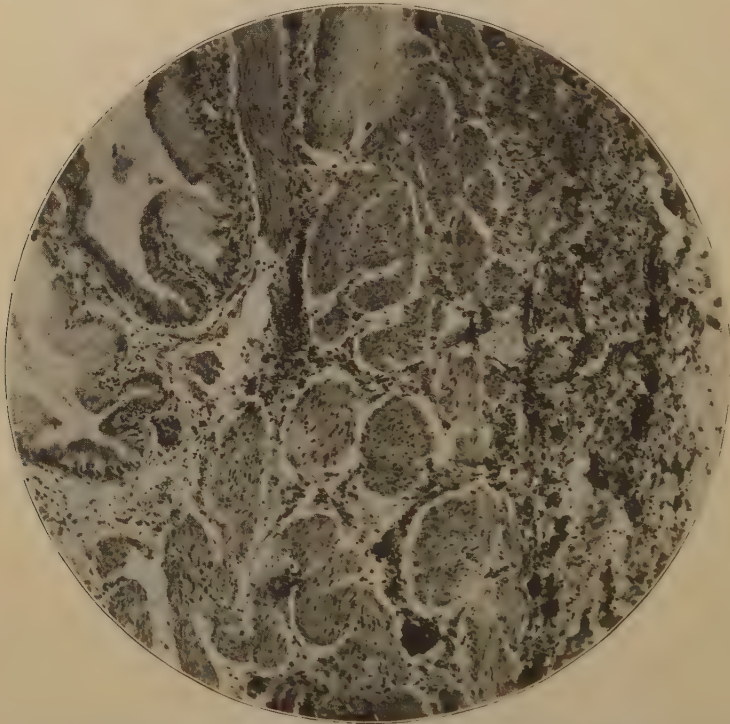


FIG. 76.—Another human gall bladder from case of cholecystitis without stones; wall extensively infiltrated with leukocytes; mucosa relatively intact.

There may be many fibrous adhesions to adjacent organs. If the wall is greatly thickened and the adhesions to other organs are unusually firm, a suspicion of carcinoma should be aroused. If there are firm adhesions to the stomach or intestine the possibility of a biliary fistula between the gall bladder and the other organ should be considered. In some cases, particularly in some of those associated with a stone in the common duct, the gall bladder may be converted into only a small mass of scar tissue. In such cases

it may be so small as to cause difficulty in finding it at operation. In the less severe cases of chronic cholecystitis the gall bladder may show only a slight change in color toward a gray, may be only slightly thickened, or it may present only a few fibrous adhesions between its under surface and some other organ. Sometimes the pathological changes are so slight that it seems difficult to understand how the organ could be responsible for the symptoms present even in those cases in which cholecystectomy relieves the symptoms. When the gall bladder is opened the mucosa in some cases will be

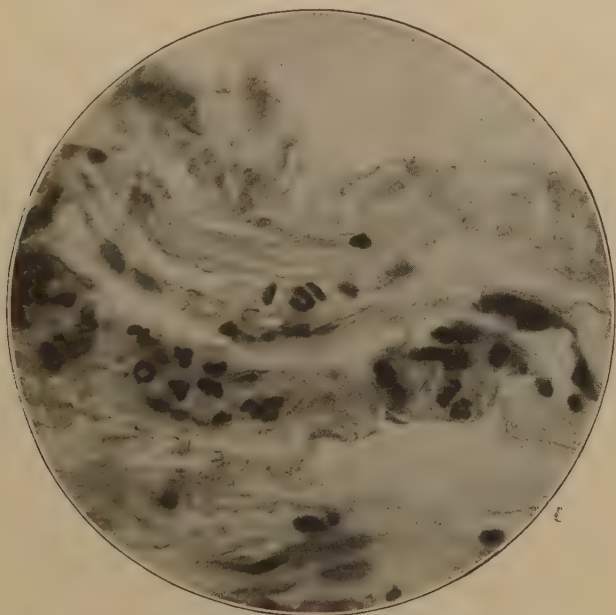


FIG. 77.—High-power magnification of Fig. 76 showing polymorphonuclear leukocytes far out in the wall of the gall bladder.

seen to be papilliform, but in the advanced and most fibrous cases it will be found to be unusually flattened. Its color may be deep red or purple and it may be swollen from edema. Edema of the whole wall may be a striking phenomenon; even on cutting through dense fibrous tissue the cut surface may exude a large quantity of edematous fluid. Stones are frequently present and the mucosa may show ulcers in places where it has been in contact with calculi. Various degrees of acute inflammation may be added to the chronic inflammatory condition. If the cystic duct has long been obstructed before the advent of a large amount of fibrous tissue of the wall of

the gall bladder the condition of *hydrops* may be present in which the gall bladder is greatly dilated and filled with a thin, white glairy, viscid fluid which is the mucoid secretion from the wall of the organ. If bile is present, it may be either dark and tarry or much lighter, even golden and thinner. Bile of the latter sort is usually found only in conditions of more advanced fibrosis of the wall; and since it closely resembles hepatic bile in appearance it

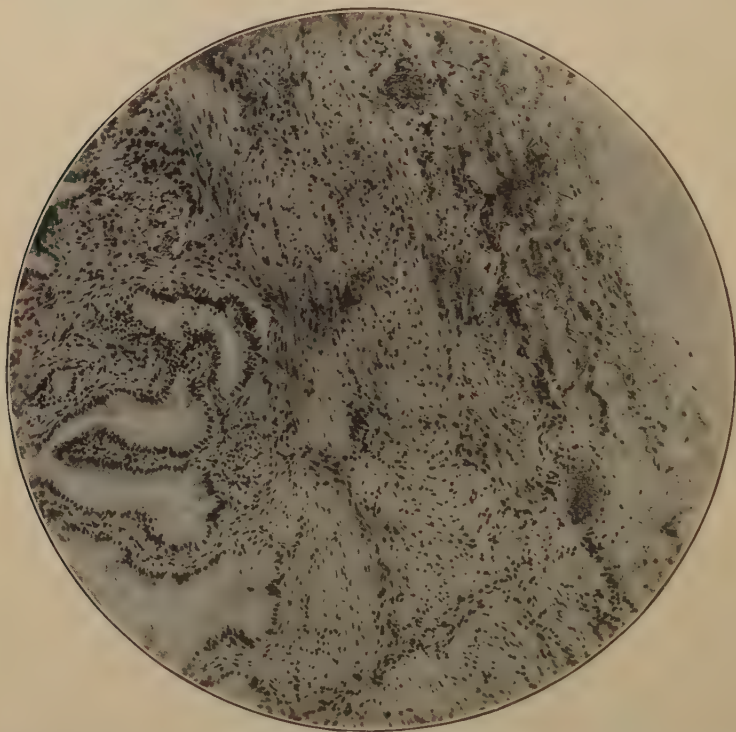


FIG. 78.—Another human gall bladder; cholecystitis without stones; mucosa relatively intact, but in outer layers of wall there is rather extensive leukocytic infiltration.

probably indicates that the concentrating mechanism of the gall bladder has been destroyed by the severe damage to its wall. In support of this idea is the additional fact, discussed elsewhere, that cholecystographic examination of such gall bladders almost invariably results in a failure to obtain a shadow. As regards the presence of thick tarry bile in cases of chronic cholecystitis, it is obvious from analogous reasoning that this finding must indicate that the concentrating function is well preserved and that this occurrence is con-

sistent with only the less severe grades of chronic cholecystitis. Kirklin<sup>1</sup> has suggested that in cases of hypertrophied villi from chronic inflammation and in the presence of papillomata the concentrating function might be even greater than normal, a state of affairs which might lead not only to the production of more concentrated bile but also to the obtaining of cholecystograms which might be regarded as normal. Further experience will be necessary to decide these points. It should be stated, however, that villi hypertrophied from inflammation which are edematous and somewhat

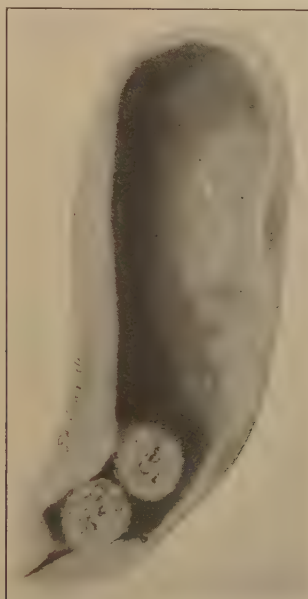


FIG. 79.—Chronic cholecystitis and cholelithiasis with carcinoma of the gall bladder in the region of the ampulla.

fibrosed may be less able to absorb fluid than the normal villi which may be actually smaller.

On *microscopic examination* of the more advanced cases the whole wall of the gall bladder is seen to be invaded with lymphocytes and plasma cells and varying numbers of polymorphonuclear leukocytes, depending on the amount of acute inflammation present. If calculi are present this cellular infiltration is likely to be most abundant in and immediately beneath the mucous membrane. In other cases, however, it is often seen most conspicuously in the

<sup>1</sup> Kirklin, B. R.: Personal communication.

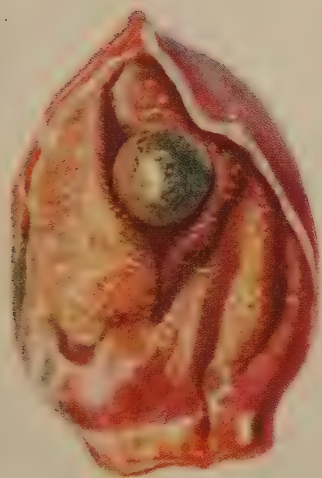


deeper layers of the wall. Granulation tissue is abundant, and in the most advanced cases the muscle and elastic tissue are practically entirely converted into fibrous tissue. In the moderately advanced cases the depressions between the villi are often much deepened, and they often give in microscopic sections the appearance of glands beneath the mucosa. The epithelial cells are frequently distended with mucin. In these moderately advanced cases the cellular infiltration of the deeper layers of the wall may be chiefly focal. The capillaries also are for the most part dilated. Large collections of fat in the subserous and muscular coats are common.

**The Strawberry Gall Bladder.**—This interesting and striking condition was apparently first emphasized and given clinical importance by Moynihan. To MacCarty, however, we are indebted for the very descriptive name. In this condition yellow specks are present on the red mucosa, giving an appearance which when marked strongly resembles a ripe strawberry. The entire mucosa is not always involved. (Plate III.) Boyd has devoted much study to this interesting type of lesion of the gall bladder. He has the opinion that the yellowish material is an ester of cholesterol and that it is of a similar nature to the lipoid occurring in the adrenal cortex and the corpus luteum of the ovary. He thinks that cholesterol is normally absorbed from the gall bladder and that if something interferes with the normal absorption the strawberry gall bladder results. He thinks, moreover, that the most probable factor in preventing the normal absorption is chronic infection. He thus places this type of gall bladder in the group of those due to a chronic cholecystitis. He presents evidence also in favor of the view that the nuclei of gall stones may sometimes be polypoid masses of epithelium, heavily laden with this cholesterol ester which have become broken off and discharged into the lumen of the gall bladder. The lipoid material when stained with Scharlach R or some similar fat stain in frozen sections presents beautiful pictures. It may be seen, however, when an unstained frozen section is examined under an ordinary microscope with the diaphragm well closed; by this means it appears as dark, almost black, masses. Under the high power the acicular crystals can be made out. The distribution of the lipoid is not always the same. In some cases it is limited to the surface epithelium, situated chiefly at the bases of the cells. In other cases it is scattered throughout the stroma, both lying free and contained within wandering cells.

**Typhoid Carriers.**—A special form of chronic infection of the gall bladder, namely, that associated with the chronic typhoid

PLATE III



Cholesterosis (Strawberry Gall Bladder) with Stone.



carrier state, deserves special mention. It is now well known that in the majority of instances typhoid carriers harbor living typhoid bacilli in their gall bladders, from where they are discharged into the intestine and eliminated in the feces. An extensive discussion of this whole question, together with the literature on the subject, is to be found in the work of Gay.<sup>1</sup> Some of these gall bladders, even though they harbor living typhoid bacilli, show little or no gross evidence of disease. But, at least microscopically, evidences of chronic cholecystitis, such as lymphocytic invasion of the wall, etc., can be found. Removal of the gall bladder in such cases often relieves the patient from being a chronic carrier. Such a favorable result, however, cannot always be expected, because in some cases there are foci of organisms elsewhere than in the gall bladder. The only statistics on this aspect of the question which we have been able to find are those of Bersch,<sup>2</sup> published in 1926. He reported 5 cases of typhoid carriers in which the gall bladder was removed. The stools of all became free of typhoid bacilli. One case, dying of tuberculosis three months after the cholecystectomy, was examined postmortem, and no typhoid bacilli were found in cultures taken from any part of the body.

A discussion of the chronic specific infections of the gall bladder, such as tuberculosis, syphilis and actinomycosis, together with the parasitic diseases is given in Chapter V.

**Pancreatitis as a Complication of Cholecystitis.**—It has long been an observation of pathologists and surgeons that sometimes in association with a chronic cholecystitis, especially if calculi are present, an enlargement of the head of the pancreas is found. This condition is probably not nearly so frequent as some surgeons believe, but yet it occurs often enough to establish it as a definite complication or sequel of cholecystitis. In well-established cases the head of the pancreas is not only enlarged but abnormally firm. It may be so hard that it is mistaken for carcinoma. Microscopically this condition is essentially a chronic interlobular pancreatitis, marked by an increase of the fibrous tissue between the lobules but with little fibrosis of the lobules themselves or of the tissue between the acini. Marked atrophy of the acini may occur as well as interference with or even loss of the external secretion of the pancreas with resultant digestive disturbances. Even pancreatic cysts may be formed as a result of the obstruction of the ducts. The islands of Langerhans

<sup>1</sup> Gay, F. P.: *Typhoid Fever Considered as a Problem of Scientific Medicine*, 1918, the Macmillan Company, New York, p. 114.

<sup>2</sup> Bersch, E.: *Zur Pathologie und Therapie der Typhusbazillenträger*, *Med Klin.*, 1926, **22**, 409.



are seldom involved, however; and consequently there is no glycosuria.

The pathogenesis of this type of pancreatitis has aroused much discussion. Klippel and Lefas<sup>1</sup> in 1899 were apparently the first to suggest a lymphatic spread from the gall bladder as an origin of this condition after mentioning the three other ideas which were then current, namely, the hematogenous origin, the spread by continuity from the common duct and the ascending route from the duodenum. Maugeret's<sup>2</sup> work in 1908 lent additional support to the idea of a lymphatic origin from the gall bladder as did also the work of Arnsperger.<sup>3</sup> In this country, however, the idea owes its popularity largely to its vigorous championing by Deaver and by Deaver and Sweet.<sup>4</sup> In work reported by one of us (Graham) with Peterman<sup>5</sup> in 1922, on the basis of experiments in which we produced this type of pancreatitis following the production of experimental cholecystitis, we concluded that we had obtained evidence which supported the idea of a lymphatic spread. Archibald,<sup>6</sup> however, has opposed this theory since 1919. He has considered this type of pancreatitis to be due to a regurgitation of bile into the pancreas, after a closing off of the common entrance of the bile and pancreatic ducts into the duodenum. He has thought that sometimes this closing off is accomplished by a spasm of the sphincter of Oddi. Recently Kaufmann,<sup>7</sup> under Archibald's direction, has reopened the subject experimentally and has given a good review of the literature. He repeated our experiments and by so doing he obtained a pancreatitis of the type under consideration, but he has concluded that the infection was carried to the pancreas by the blood stream instead of by the lymph. He concludes furthermore that as yet at least there is no satisfactory evidence that this type of pancreatitis is ever

<sup>1</sup> Klippel, M. and Lefas, E.: *Maladies du Pancreas*, Arch. gén. de méd., 1899, **184**, 74.

<sup>2</sup> Maugeret, R.: *Cholécyste-Pancréatite*, Thèse, Paris, G. Steinheil, 1908.

<sup>3</sup> Arnsperger: *Die Entstehung der Pankreatitis bei Gallensteinen*, München. med. Wehnschr., 1911, **58**, 729.

<sup>4</sup> Deaver, J. B. and Sweet, J. E.: *Prepancreatic and Peripancreatic Disease: with a Consideration of the Anatomic Basis of Infection from the Gall Bladder to the Pancreas*, Jour. Am. Med. Assn., 1921, **77**, 194.

<sup>5</sup> Graham, E. A. and Peterman, M. G.: *Further Observations on the Lymphatic Origin of Cholecystitis, Choledochitis and the Associated Pancreatitis*, Arch. Surg., 1922, **4**, 23.

<sup>6</sup> Archibald, E.: *The Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common Duct Sphincter*, Surg., Gynec. and Obst., 1919, **28**, 529; also Archibald, E., and Gibbons, E. C.: *Further Data Concerning the Experimental Production of Pancreatitis*, Trans. Am. Surg. Assn., Philadelphia, 1921, **39**, 96; Ann. Surg., 1921, **74**, 426.

<sup>7</sup> Kaufmann, M.: *An Experimental Study of the Lymphatic Theory of Pancreatitis*, Surg., Gynec. and Obst., 1927, **44**, 15.

lymphogenous in origin. The real question of course is whether or not there is a lymph stream from the gall bladder actually into the pancreas. Kodama's study of the lymphatics of this region carried out recently in our laboratory, to which reference was made in Chapter I, indicate that there is no lymphatic stream normally which runs from the gall bladder into the substance of the pancreas. We feel therefore that we were probably in error in our former conclusion that we had demonstrated a lymphogenous origin of pancreatitis from a cholecystitis. If, however, the gall bladder becomes adherent to the pancreas then infection can pass through the adhesions into the substance of the gland.

The condition sometimes known as acute hemorrhagic pancreatitis or pancreatic necrosis which occasionally occurs as a sequel of cholecystitis is discussed in Chapter V.

## CHAPTER IV.

### GALL STONES.

**Introduction.**—The subject of cholelithiasis has attracted the attention of innumerable investigators who have reported their experiments and clinical findings in a vast number of books and journals. It is impossible in a discussion of the subject to do more than mention some of the important articles. While the succeeding paragraphs are in a large part concerned with the etiology and pathology of gall stones, their inter-relationship with the biliary tract and bodily states are considered. It is recommended that the reader peruse the chapter on the Physiology of the Gall Bladder in order that he may have a clearer idea of the factors involved in the formation of gall stones.

#### HISTORICAL SUMMARY.

The historical aspects of our knowledge of the gall bladder with particular reference to our knowledge of gall stones has been discussed in an excellent article by Hoppe-Seyler.<sup>1</sup> Most of this present historical survey is taken from his work. His summary, however, is concerned only with the knowledge of the gall bladder which was current among Europeans. He makes no mention of the early Jewish writings on this subject which are quoted in Chapter I of this book. It is very striking that the early European medical writers seem to have had little or no knowledge of gall bladder disease either in human beings or domestic animals. There is particularly no mention at all of anything which could be considered as gall stones in the early European writings. The first mention of them by a European writer seems to be that by Antonius Benivenius, who died in 1592. He described gall stones that were seen in the gall bladder and in the liver of a woman who had suffered from pain in the abdomen. Hoppe-Seyler thinks that the remarkable absence of comment on gall stones by the early European anatomists must signify that gall stones were much less common in those days than they are now and he suggests that perhaps the different methods of living of the ancients as compared with modern methods may have some bearing on the question.

Following the description of the gall stones noted by Antonius Benivenius, Fernelius, in 1554, gave a description not only of gall stones but also of the symptoms which they may produce. He knew, for example, that obstruction of the common bile-duct may lead to a swelling of the gall bladder, a

<sup>1</sup> Nothnagel's Encyclopedia of Practical Medicine, American edition, Diseases of the Liver, Pancreas and Suprarenal Glands, 1903, W. B. Saunders Company, Philadelphia, p. 525.

white discoloration of the feces and the passage of dark urine, and also that when the hepatic duct is obstructed the gall bladder is empty. Columbus, who died in 1557, stated that a postmortem examination made of the body of the Jesuit General Ignatius de Loyola, showed numerous concretions in the liver, portal vein, kidneys and lung. The assumption has generally been made that this anatomist confused the portal vein with branches of the bile-ducts and that the stones were probably within the bile-ducts instead of within the portal vein.

Johann Kentmann, in 1565, in an epistle reprinted in Gessner's work (*De omnium rerum fossilium genere*) described gall stones of different sizes and shapes. He noted that when they were multiple they were likely to have an angular shape and that the broken surface of a stone showed it to be composed of circular structures. Forestus held the opinion that gall stones are formed under conditions in which the gall bladder is not properly emptied and the cystic duct is occluded. He also stated that Arculanus of Verona (1457) was the first to attribute icterus to an occlusion of the bile-duct. Glisson (1654) in his important book described gall stones in cattle and also gives an interesting description (Chapter XXX, page 265) of his own case in which he pictures an attack of colic associated with icterus and pain radiating into the region of the clavicle. Since he could not demonstrate the presence of nerves in any other parts than in the hepatic capsule and in the walls of the bile passages he considered that the pain must originate in the bile-ducts. Wepfer (1658), making use of Glisson's studies, concluded that the bile is formed in the liver and is poured through the bile passages and the common duct into the intestine. He concluded also that icterus can never occur as the result merely of occlusion of the cystic duct unless the ductus choledochus is occluded at the same time. Ettmüller in his dissertation entitled "*De ictero flavo, nigro et albo*" (*Oper. med.*, Tom. II, page 1, Colleg. pract., Sect. XVII, Cap. IV, page 442) gives a remarkably accurate clinical picture of biliary tract disease. He speaks of pain in the precordial region which appears with icterus and is accompanied by nausea, difficult respiration and a reddish color of the urine. He states that fever is often present and in many cases pain in the right hypochondrium, which may either be readily removed or be very difficult to cure, or, lastly, may be removable but shows a tendency to recur. In the latter type, he said, stones were commonly found in the gall bladder. He also noted that colic and icterus are sometimes seen after child-birth and that icterus frequently follows the attack of colic and that it is frequently the result of an obstruction to the flow of bile into the intestine or of insufficient secretion of bile by the liver as is seen from the fact that icterus may occur without an obstruction in the bile passages following fever, the bite of wild animals, abuse of blood-letting, etc. He observed further that icterus does not necessarily always occur in cases of gall stones. He was convinced that the gall bladder could be extirpated without endangering the life of the animal and he quotes the important experiment of one of the students in Leyden who removed the gall bladder from a dog without observing any bad results. He considered that icterus was due to obstruction of the common bile-duct which caused a regurgitation of bile into the blood. He also states that there is no remedy for gall stones.

Sydenham, according to Hoppe-Seyler, is frequently credited with discoveries that have thrown light on the pathology of gall stones. As a matter of fact, however, he considered gall-stone colic as a symptom of hysteria and he described its occurrence in female subjects, who were suffering from other forms of hysterical seizures. (*Prax. med.*, Sect. IV., Chap. VII, Par. 16.) Vater (1722) attributed the fever, which often occurs after gall stones are passed, to an irritation of the nervous system caused by the



impaction and the passage of the stone through the narrow lumen of the bile passages. Friedrich Hoffmann, in his *Medicina Rationalis Systematica* attributed the formation of gall stones to stagnation of bile and he concluded eating small amounts and at long intervals favored their formation. Haller is quoted by Hoppe-Seyler as having shown definitely that the bile is not secreted in the gall bladder but in the liver and that certain substances can exercise a direct chemical irritation in the gall bladder and the ductus choledochus causing contractions of these parts. He searched for muscle fibers in these organs but could not demonstrate them. Morgagni in his epoch-making work (*De sedibus et causibus morborum*) makes an excellent presentation of the subject of cholelithiasis. According to him, occlusion of the bile passages is the result of a simple contraction of the ducts, a thickening of their mucous lining, compression of the passages by swollen glands, etc. This occlusion is always followed by icterus. If the cystic duct alone is occluded icterus is not observed. He mentions as predisposing causes, the age of the subject, sedentary habits and other factors. He gives a detailed description of the appearance and structure of gall stones and he is opposed to the view, prevalent at that time, that the dark stones are seen in old people and light ones in young subjects. He also has the opinion that irritation of the glands of Malpighi in the wall of the gall bladder is another predisposing factor in the formation of gall stones. Pouilletier de la Salle is stated by Hoppe-Seyler to have been the first investigator who succeeded in isolating cholesterin. This occurred in about the middle of the eighteenth century.

**Incidence.**—The incidence of the occurrence of gall stones found in routine postmortem examinations varies from 5 to 20 per cent. Mentzer<sup>1</sup> performed 633 consecutive necropsies at the Mayo Clinic and found 21.67 per cent of the adults had gall stones. Hansen<sup>2</sup> states that gall stones were found in 24.7 per cent of 392 adult cadavers. Mosher<sup>3</sup> found in a study of 1655 necropsy records at the Johns Hopkins Hospital that 8 per cent of the patients dying in the fourth decade had gall stones. The incidence of gall stones in the fifth and sixth decades was 13 per cent. Gall stones occurred more frequently in the female than in the male bodies. C. H. Mayo<sup>4</sup> states that 70 per cent of cases of gall-bladder disease have stones. In 282 gall bladder operations performed by Stanton<sup>5</sup> gall stones were present in 216 patients, or 77 per cent. Fallon<sup>6</sup> analyzed 1103 operations on the gall bladder and bile-ducts and found 90 per cent

<sup>1</sup> Mentzer, S. H.: The Pathogenesis of Biliary Calculi, Arch. Surg., 1927, **14**, 14.

<sup>2</sup> Hansen, S.: Formation of Gall Stones in the Liver, Hospitalstidende, Copenhagen, 1926, **69**, 217.

<sup>3</sup> Mosher, C. D.: (Abstract) The Frequency of Gall Stones in the United States, Johns Hopkins Hosp. Bull., 1901, **12**, 253.

<sup>4</sup> Mayo, C. H.: Gall Stones and Diseases of the Gall Bladder, Am. Surg. Assn., 1925, **81**, 955.

<sup>5</sup> Stanton, E. M.: The Stoneless Gall Bladder, Jour. Am. Med. Assn., 1926, **87**, 2160.

<sup>6</sup> Fallon, M. F.: Analysis of One Thousand One Hundred Operations on Gall Bladder, Boston Med. and Surg. Jour., 1927, **196**, 171.

were for gall stones. Deaver and Bortz<sup>1</sup> found that 50 per cent of 903 patients with gall bladder disease had gall stones.

Cholelithiasis is a common affection in America and Europe, and said by Rolleston<sup>2</sup> to be rare in Russians, Indians and Japanese. Stones are found much less frequently among the negroes than among the whites in America. Gall stones are comparatively seldom found in domesticated animals.

**Sex.**—Cholelithiasis is found more commonly in women than in men. The ratio between the sexes is usually stated as stone being present in women two to five times more frequently than in men.

**Age.**—The incidence of gall stones increases as age advances. The majority of patients with cholelithiasis are over thirty years of age and less than 1 per cent are under twenty years. There have been a few reports of gall stones in the newly born. Snyder<sup>3</sup> reviewed the literature concerning cholecystitis and cholelithiasis in young children and found reported from the years 1722 to 1922 approximately 80 cases of gall-bladder disease in children.

### CHEMICAL CONSTITUENTS OF GALL STONES.

Cholesterol and bilirubin-calcium are the chief constituents of gall stones. Free calcium carbonate is also important. Calcium also occurs in combination with oxidation products of bilirubin. Metallic mercury, copper, iron and other metals have been found in stones.

**The Bile Salts.**—Bile acids do not appear in the free state in the bile, but as sodium salts, and are an exclusive product of liver metabolism. They are derived from cholic acid and combine with glycine and taurine to form the sodium salts of glycocholic and taurocholic acids. Human bile contains relatively a small amount of taurocholic acid. The bile salts, as other solids in the bile, are found in greater concentration in bile obtained from the gall bladder than from a biliary fistula. The usual analyses show that in 100 parts of gall-bladder bile there are 80 to 90 parts water and 10 to 20 parts solids. The bile salts comprise over half of the solids. Bile salts are of especial significance in the formation of gall stones because of their remarkable solvent action on cholesterol. This solvent

<sup>1</sup> Deaver, John B. and Bortz, E. L.: Gall Bladder Disease: A Review of 903 Cases, *Jour. Am. Med. Assn.*, 1927, **88**, 619.

<sup>2</sup> Rolleston, Sir H.: The Etiology and Medical Treatment of Gall Bladder Disease, *Lancet*, June 6, 1925, p. 1207.

<sup>3</sup> Snyder, C. C.: Cholecystitis and Cholelithiasis in Young Children, *Jour. Am. Med. Assn.*, 1925, **85**, 31.

property depends on the cholic acid content which is chemically closely related to cholesterol.

Although the bile salts are one of the chief constituents of bile, they are found in bile stones only in minute quantities.

**The Bile Pigments.**—Bilirubin is considered the mother substance of all bile pigments and is the pigment that gives normal bile its yellowish appearance. It is held in solution in bile by the alkaline bile salts, and since bilirubin is acid in nature, it can combine with alkalis to form salts. The most important compound that bilirubin forms in relation to gall stones is the calcium compound. The calcium and bilirubin of normal bile do not normally combine readily because of the presence of bile salts. However, bilirubin calcium is a frequent constituent of human gall stones. Small quantities of bilirubin and its derivatives are occasionally found in calculi in a free state.

Biliverdin, which is produced by the oxidation of bilirubin, occurs in the bile of man and imparts to it a green color. Biliverdin also forms compounds with calcium and is found in stones.

Small quantities of various biliary pigments are found which are probably not normal constituents of bile but are oxidation products of bilirubin and are found chiefly in gall stones.

**The Calcium of the Bile.**—Calcium compounds play an important rôle in the formation of calculi. The administration of large quantities of calcium salts either by mouth or intravenously does not seem to alter the output of calcium in the bile. The greater part of the calcium in the bile is probably secreted by the liver and possibly by the lining of the bile-ducts. Drury<sup>1</sup> collected the bile daily from the hepatic ducts of dogs and found the concentration of calcium to be constant. He made the further important observation that the normal gall bladder does not secrete calcium into the bile as some have supposed, but that it absorbs it from hepatic bile. The solubility of the calcium is modified by changes of reaction of the bile. Ippongsugi<sup>2</sup> has confirmed the essential facts reported by Drury and others. Fowweather and Collinson<sup>3</sup> determined the blood calcium in 58 cases of gall stones and found that 19 (32.8 per cent) showed definitely raised values, while 5 (8.6 per cent) showed high

<sup>1</sup> Drury, D. R.: Studies on the Total Bile. VII. Conditions Influencing the Calcium Content of the Bile, *Jour. Exper. Med.*, 1924, **40**, 797.

<sup>2</sup> Ippongsugi, T.: Experimental Studies on Calcium Metabolism. IV. On the Calcium Excretion in Bile, *Mittel. allg. Path. u. path. Anat.*, 1926, **3**, 303.

<sup>3</sup> Fowweather, F. S. and Collinson, G. A.: Chemical Changes Associated with Gall Stones: Relation between Gall Stones and Hypercholesterolemia, *British Jour. Surg.*, 1927, **14**, 583.

normal values. Eleven of the 19 cases showing raised blood calcium occurred among 35 patients with increased blood cholesterol.

**The Fats and Soaps of the Bile.**—Fats and soaps are normally found in bile as margarin, stearin and palmitin or their compounds. The quantity present in bile varies considerably, but is always greater when the diet contains fat. Fats and soaps are solvents of cholesterol. Fatty acids and soaps frequently are present in biliary calculi.

### CLASSIFICATION OF BILIARY CALCULI.

The usual classification of biliary calculi, according to their chemical composition is based on the one given by Naunyn,<sup>1</sup> or the one given by Aschoff and Bacmeister.<sup>2</sup> A slight modification of these classifications would seem to simplify the grouping of biliary calculi. There are, probably, essentially only two types, which may be subdivided, the cholesterolin stone and the bilirubin-calcium stone.

**I. Cholesterol Stone.**—1. **Pure Cholesterol Stone.**—These stones may contain as much as 98 per cent cholesterol. Their crystalline structure is well marked, but they show no signs of stratification, but appear to be a conglomerate mass of cholesterol crystals. The stones are firm, yellowish-white, vary in size from a cherry to an English walnut, and may be oval or round.

2. **Laminated Cholesterol Stone.**—These stones may contain 75 to 90 per cent of cholesterol, which is arranged in a stratified manner about the nucleus. They resemble pure cholesterol stones in form and size, except that they are frequently faceted. These stones contain small amounts of calcium salts of pigments, which are also deposited in layers.

3. **The Common or Gall Bladder Stone.**—This is essentially a cholesterol stone composed of cholesterol and bile pigment. They are of various colors, are generally faceted, seldom exceed a cherry in size, and are without gross crystalline formation. Traces of metals are present. They have a stratified structure with usually a firm shell enclosing a softer pulpy nucleus in which frequently can be found a central cavity containing a yellowish alkaline fluid. The majority of gall stones belong to this group.

<sup>1</sup> Naunyn, B.: *Klinik der Cholelithiasis*, Verlag von F. C. W. Vogel, Leipzig, 1892, translation by A. E. Garrod, New Sydenham Soc., 1896; *Die Cholelithiasis*, G. Fischer, Jena, 1921; *Die Gallensteine, ihre Entstehung und ihr Bau*, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1921, **33**, 1.

<sup>2</sup> Aschoff, L. and Bacmeister, A.: *Die Cholelithiasis*, Verlag von Gustav Fischer, Jena, 1919.



**II. Bilirubin Calcium Stone.**—These stones are usually small, varying in size from a grain of sand to a pea. They consist chiefly of bilirubin calcium mixed with mucus, and rarely contain cholesterol. There is a wax-like, irregular, blackish-brown form, and a harder, nodular form of steel-gray or black color. These stones are frequently of intra-hepatic origin and may form casts of the ducts. Occasionally these stones may occur singly or in a group of three or four, and may attain a large size. This latter type contains some cholesterol.

**III. Rarer Forms of Biliary Calculi.**—1. **Imperfectly Crystallized Cholesterol Stone.**—These cholesterol stones form about a nucleus of bilirubin calcium without stratification.

2. **Calcium Carbonate.**—This form of stone is rare in man, but common in animals. It occurs in a free state or combined with biliary pigments.

It will be seen from the above classification that biliary calculi contain in varying proportions all constituents of bile. Cholesterol forms the chief part of most biliary stones. Calcium salts of the bile pigments are always present. Usually inorganic calcium salts are present along with small amounts of fats, soaps, lecithin, mucus, etc. It is interesting to find that bile salts, the chief constituent of bile, are present in only minute quantities.

### THE SHAPE OF A BILIARY CALCULUS.

The shape of a biliary calculus is largely dependent on the seat of its development, on the number present and on its chemical constitution. Single stones may be oval, spherical, cylindrical, and at times they form a cast of the lumen of a duct. Multiple calculi tend to have the same structure and constitution. Several stones in the gall bladder or large ducts are subject, while soft, to mutual pressure and become polyhedral in shape. These flattened smooth surfaces are known as facets. Some believe that facets are not formed by pressure, but by friction. Solitary stones or those occurring with only one or two others, usually have a rough surface.

### DISPOSING CAUSES OF GALL STONES.

**Presence of a Nucleus.**—The production of cholelithiasis may be accomplished by a variety of disposing and exciting causes. Usually there is present a nucleus of some substance for the formation of a concretion different from the substance that is to be deposited in the form of a stone. The nucleus of a gall stone is more frequently

a mass of bile pigment, but may be desquamated cells, blood, bacteria, mucus, precipitated proteins, or a foreign body. Substances crystalize out of solution upon a nucleus and are held together in a concentric or laminated structure by organic matter. Consequently concretions are a mixture of colloids and crystalloids. Substances suitable to act as nuclei may be intrinsic or extrinsic of the biliary tract in origin. Pure cholesterol stones usually do not possess a nucleus as do the cholesterol pigment calcium stones. Boyd,<sup>1</sup> Stewart<sup>2</sup> and Mentzer<sup>3</sup> believe that papillomata of the gall bladder are important in the formation of cholesterol stones. They believe that these cholesterol-laden polypi break off from the wall of the gall bladder and act as nuclei for the formation of stones.

**Stasis of Bile.**—The stasis or stagnation of bile in the gall bladder and ducts is considered by many as both a disposing and an exciting cause of cholelithiasis. Clinical observation has shown that sedentary habits, obesity, pregnancy, lack of exercise and organic obstruction dispose to the stagnation of bile in the gall bladder, which perhaps in turn favors the multiplication of bacteria, if present in the bile. The presence of the bacteria favors stone formation. However, organisms may be present in the bile and not produce a cholecystitis or cholelithiasis. The normal low gall bladder is thought by some clinicians to give rise to symptoms in some instances and to be more susceptible to disease than those which are higher, and which presumably empty more rapidly. But in spite of this opinion, the prevailing bodily habitus found in gall-bladder disease is not the visceroptotic. It would seem, therefore, as if visceroptosis and even a moderate amount of stasis of bile does not predispose to disease of the gall bladder. A more extensive discussion of this question is given in Chapter VII.

**Diet.**—The rate of secretion of bile by the liver and the rate of its flow from the biliary tract into the duodenum are greatly influenced by diet. Long intervals between meals and the absence of fats or other substances which stimulate the emptying of the gall bladder lead to stagnation of bile in the gall bladder and so favor physical changes and infection of bile. Foods which are rich in cholesterol seemingly may produce a hypercholesterolemia which may favor the disposition of stones in the biliary tract. Restriction of the quantity of fluids taken by mouth would tend to produce stasis in the gall bladder and ducts by reducing the amount of bile secreted.

<sup>1</sup> Boyd, William: Studies in Gall Bladder Pathology, *British Jour. Surg.*, 1923, 10, 337.

<sup>2</sup> Stewart, M. J.: Xanthoma and Xanthosis, *British Med. Jour.*, 1924, ii, 893.

<sup>3</sup> Mentzer, S. H.: The Pathogenesis of Biliary Calculi, *Arch. Surg.*, 1927, 14, 14.

Whitaker<sup>1</sup> suggests that too frequent meals may keep the gall bladder in a partially collapsed state over considerable periods of time. This state may favor concentration and precipitation of bile which would be conducive to stone formation.

**Pregnancy.**—It is estimated that 80 to 90 per cent of females with cholelithiasis have borne children. One of the probable ways that pregnancy disposes to gall stone formation is by stasis of the biliary flow and infection. Pregnancy often necessitates a sedentary life, dislocates the intra-abdominal viscera and is usually accompanied by constipation. During pregnancy the blood contains an excess of cholesterol, which is thought by some observers to favor cholelithiasis. Mann and Higgins<sup>2</sup> have suggested that the failure of the gall bladder of the pregnant animal to empty may have a relation to the high incidence of gall stones following pregnancy in the human. Crossen and Moore,<sup>3</sup> however, procured cholecystographic evidence of normal filling and emptying of the gall bladder in females during their fortieth week of pregnancy.

**Association With Diseases of Other Organs and Systems.**—The incidence of cholelithiasis is higher in those who have cardiac disease. Likewise, pulmonary and renal disease has been said to favor cholelithiasis. The incidence of stone is apparently not increased by cirrhosis or syphilis of the liver. The relationship of diabetes mellitus and cholecystitis was studied at Barnes Hospital by cholecystography, by Tedstrom, Bond, Olmsted and Moore.<sup>4</sup> They found that the incidence of cholecystitis in the diabetic probably exceeded only slightly that found in the non-diabetic.

Mentzer<sup>5</sup> found in a postmortem study that 90 per cent of patients weighing over 220 pounds had gall-bladder disease. The incidence in adult patients weighing 110 pounds or less was only 30 per cent.

The liver, gall bladder and ducts have an intimate anatomical relationship with the intestinal tract because of their blood, lymph and nerve supply. Indigestion, constipation, peptic ulcer and appendicitis, especially, may concurrently play a prominent rôle as etiological factors of hepatitis, cholecystitis and cholelithiasis. Bacteria, especially the colon and typhoid bacilli may pass from the

<sup>1</sup> Whitaker, L. R.: The Mechanism of the Gall Bladder and its Relation to Cholelithiasis, *Jour. Am. Med. Assn.*, 1927, **88**, 1542.

<sup>2</sup> Mann, F. C. and Higgins, G. M.: Effect of Pregnancy upon the Emptying of the Gall Bladder, *Proc. Soc. Exper. Biol. and Med.*, 1927, **24**, 930.

<sup>3</sup> Crossen, R. J. and Moore, Sherwood: Application of Cholecystography in Pregnancy; not yet published.

<sup>4</sup> Tedstrom, M. K., Bond, R. C., Olmsted, W. H. and Moore, Sherwood: Cholecystography in Diabetes Mellitus, *Jour. Am. Med. Assn.*, 1926, **87**, 1603.

<sup>5</sup> Mentzer, S. H.: The Pathogenesis of Biliary Calculi, *Arch. Surg.*, 1927, **14**, 14.

intestines to the biliary tract by way of the portal vein and lymphatics. Infection may spread to the tract from adjacent organs by direct extension. It is significant that approximately 80 per cent of patients with gall stones are said to have constipation.

**Influence of Heredity.**—It is a very old idea that cholelithiasis is a hereditary disease, largely dependent on constitutional factors. Panzel<sup>1</sup> has only recently reported a case of familial cholelithiasis.

It is interesting to know, in this connection, that a patient having a congenital duplication of the gall bladder had stones in only one of the vesicles.

## THEORIES OF THE FORMATION OF BILIARY CALCULI.

**Stasis Theory.**—Stagnation of bile in the biliary tract from any cause has been considered as predisposing to the formation of stones in a preceding paragraph. It is by some considered a primary etiological factor. Naunyn<sup>2</sup> held that biliary stagnation is the first essential condition for the formation of stones in that it damaged the cells of the mucous membrane. Conversely, inflammation of the gall bladder is conducive to the stagnation of bile by tending to destroy the concentrating activity of the gall bladder and interfering with the motility of the vesicle. Whitaker<sup>3</sup> produced stones experimentally in animals by altering the normal mechanism of filling and emptying of the gall bladder so that stasis and overconcentration of bile resulted.

**Infection Theory.**—Normal bile obtained from the normal biliary tract of a healthy individual is sterile. However, bacteria readily gain entrance to the biliary tract by way of the liver, the blood-vessels and lymphatics, and perhaps occasionally by way of the common duct from the duodenum, particularly when the flow of bile is obstructed. The bile in the ducts and gall bladder above a ligature about the common duct becomes infected in a short time. It is equally important that inflammation of the wall of the gall bladder and of the ducts may follow shortly.

The theory of biliary infection for the formation of gall stones was

<sup>1</sup> Panzel, S.: Cholesterolemia, Xanthomatosis and Familial Cholelithiasis, München. med. Wehnschr., 1926, **73**, 2119.

<sup>2</sup> Naunyn, B.: Klinik der Cholelithiasis, Verlag von F. C. W. Vogel, Leipzig, 1892, translation by A. E. Garrod, New Sydenham Soc., 1896; Die Cholelithiasis, G. Fischer, Jena, 1921; Die Gallensteine, ihre Entstehung und ihr Bau, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1921, **33**, 1.

<sup>3</sup> Whitaker, L. R.: The Mechanism of the Gall Bladder and its Relation to Cholelithiasis, Jour. Am. Med. Assn., 1927, **88**, 1542.



first suggested by Galippe<sup>1</sup> in 1886, and later accepted by Naunyn,<sup>2</sup> who believes the immediate cause of the formation of stones is a mild inflammation of the mucous membrane of the ducts and gall bladder. It is now widely accepted as one of the essential factors in biliary calculi formation. However, this theory is denied by some investigators and there is some doubt if it accounts for all types of stones. Gall stones, as was pointed out by Aschoff and Baumeister,<sup>3</sup> particularly stones rich in cholesterol, are found in gall bladders whose walls show no inflammatory changes. We have noted that these gall bladders sometimes produce normal cholecystograms, denoting that there has been no interference with their concentrating activity and motility. Inflammatory changes in gall bladders seem somewhat in proportion to the amount of bile pigment in the stones.

Organisms frequently associated with the production of cholelithiasis are the colon and typhoid bacilli. Mignot<sup>4</sup> produced calculi in a guinea-pig as a result of the action of *Bacillus coli* on the gall-bladder, and these bacilli have often been demonstrated inside stones. The relation between typhoid fever and gall stones has long been known clinically. Blalock<sup>5</sup> found that 28 per cent of 888 cases of gall-bladder disease at the Johns Hopkins Hospital gave a history of typhoid fever. Both typhoid and paratyphoid bacilli have been found in calculi and they may be usually found in the gall bladder during the course of the systemic disease produced by these bacteria. The colon and typhoid bacilli are more likely to reach the liver by way of the portal vein and be excreted into the bile-ducts, and so later the gall bladder, than to reach the gall bladder as a result of an ascending infection from the duodenum. Small concretions have been produced by experimental typhoidal cholecystitis and by massive intravenous injections of other organisms. Rosenow<sup>6</sup> and others who performed these experiments demonstrated, after an injection, the presence of the organisms in the wall of the gall bladder.

Bacteria are found in the wall of the gall bladder in a majority

<sup>1</sup> Galippe, V.: *Mode de Formation du Tartre et des Calculus Salivaires; Considerations sur la Production des Calculus en general; Presence des Microbes ou de Leurs Germes dans ces Concretions*, *Compt. rend. Soc. Biol.*, 1886, **38**, 116.

<sup>2</sup> Naunyn, B.: *Loc. cit.*

<sup>3</sup> Aschoff, L. and Baumeister, A.: *Die Cholelithiasis*, Verlag von Gustav Fischer, Jena, 1909.

<sup>4</sup> Mignot, R.: *L'Origine Microbienne des Calculus Biliaires*, *Arch. gen. de Med.* 1898, **182**, 129.

<sup>5</sup> Blalock, A.: *A Statistical Study of Eight Hundred and Eighty-eight Cases of Biliary Tract Disease*, *Johns Hopkins Hosp. Bull.*, 1924, **35**, 291.

<sup>6</sup> Rosenow, E. C.: *The Etiology of Cholecystitis and Gall Stones and their Production by the Intravenous Injection of Bacteria*, *Jour. Infec. Dis.*, 1916, **19**, 527.

of the clinical cases. Huntemueller<sup>1</sup> found bacteria present in every instance in the walls of 150 diseased gall bladders removed at operation. Staphylococci were found in the majority of instances. Judd, Mentzer and Parkhill<sup>2</sup> made bacteriological studies of a portion of the wall and a specimen of bile from 200 gall bladders. Fourteen per cent of the cultures of bile were positive for bacteria. Concentrated bile was found to be an inhibitor of bacterial growth. Gall stones were positive for bacteria in 31 per cent and 40 per cent of the cultures of the wall of the gall bladder were positive. The organism most frequently found in the wall was a streptococcus. Organisms were grown in some instances from the wall of the gall bladder when there was no gross evidence of inflammation. Injection of the streptococci isolated by culture into animals produced lesions of the gall bladder or infection of the bile in 75 per cent of the instances.

If the presence of bacteria is an exciting cause of the formation of biliary calculi, they could act not only by producing inflammatory changes in the wall of the gall bladder and ducts which disturb its motility, concentrating activity, etc., but by alteration in the composition of bile. Lichtwitz's<sup>3</sup> theory for stone formation, in fact, is founded on chemical changes taking place in the bile. Rous, McMaster and Drury<sup>4</sup> found the reaction of bile in the gall bladder to be a factor in the pathogenesis of calculi. In their study of the problem with permanently aseptically intubated dogs they frequently observed stones to form upon the glass and tubing. Rous, McMaster and Broun<sup>5</sup> do not believe that infection is an essential factor in cholelithiasis, though it may frequently be a determining factor by damaging the mucous membrane of the ducts and gall bladder, causing a desquamation of cells, and altering their ability to get rid of the débris. This débris favors the deposit of solids and may become nuclei of stones.

<sup>1</sup> Huntemueller: Die entzündlichen Erkrankungen der Gallenwege vom Standpunkte des Bakteriologen, *Klin. Wehnschr.*, 1924, **3**, 349.

<sup>2</sup> Judd, E. S., Mentzer, S. H. and Parkhill, E.: Bacteriologic Study of Gall Bladders Removed at Operation, *Am. Jour. Med. Sci.*, 1927, **173**, 16.

<sup>3</sup> Lichtwitz, L. Experimentelle Untersuchungen über die Bildung von Niederschlägen in der Galle, *Deutsch. Arch. f. klin. Med.*, 1907, **92**, 100.

<sup>4</sup> Rous, P., McMaster, P. D. and Drury, D. R.: The Genesis of Gall Stones in the Dog, *Proc. Soc. Exper. Biol. and Med.*, 1923, **20**, 6; Observations on Some Causes of Gall Stone Formation: I. Experimental Cholelithiasis in the Absence of Stasis, Infection and Gall Bladder Influences, *Jour. Exper. Med.*, 1924, **39**, 77; II. On Certain Special Nuclei of Deposition in Experimental Cholelithiasis, *ibid.*, 1924, **39**, 97; III. The Relation of the Reaction of the Bile to Experimental Cholelithiasis, *ibid.*, 1924, **39**, 403.

<sup>5</sup> Rous, P., McMaster, P. D. and Broun, G. D.: The Experimental Production of Gall Stones, *Proc. Soc. Exper. Biol. and Med.*, 1922, **20**, 128.

In summary it may be stated that the exact part which bacteria play in the etiology of biliary calculi is uncertain at present. Whether the infection of bile or the wall of the gall bladder by bacteria is the cause or in some instances the result of the formation of stones, remains to be decided by further experimental work.

**The Role of Cholesterol.**—Cholesterol occurs normally in many tissues of the body, is a constant variable constituent of the bile of man, and forms the greater part of most gall stones. It is found in a higher concentration in the bile in the gall bladder than in bile which has not entered the organ. Cholesterol is insoluble in water, but is soluble in alcohol, ether, and chloroform. It is held in solution in bile by fats, soaps and bile salts.

Much remains to be learned regarding cholesterol, its normal metabolism and the part it plays in disease. Quantitative determinations of the lipid in the blood and bile are subject to many varying conditions and are made by several different methods. Heilbron, Kamm and Morton<sup>1</sup> have even concluded that cholesterol is two compounds. They find by a study of its absorption spectrum that ordinary purified cholesterol contains another compound in small quantity which can be collected in the least soluble fraction.

Though a large number of determinations of the total cholesterol content of blood or serum have been made in pathological conditions, comparatively few determinations have been made on normal individuals. Such a study has recently been made by Gardner and Gainsborough,<sup>2</sup> of normal fasting medical students, varying in age from eighteen to fifty-eight years. They conclude that normal individuals differ widely in the total cholesterol content of their plasma. Their average determination of the total cholesterol content, comprised of both free and cholesterol esters, is 0.16 gm. cholesterol in 100 cc. of plasma.

The varying results of cholesterol determinations by different investigators must be considered when diagnostic significance is attached to the figures. However, it is generally agreed that there is an increase of the blood cholesterol in certain forms of nephritis, occasionally in diabetes, in the later months of pregnancy and in some infections. Its metabolism is presumed to be associated with the endocrine glands, particularly the suprarenal cortex.

<sup>1</sup> Heilbron, I. M., Kamm, E. D. and Morton, R. A.: The Absorption Spectrum of Cholesterol and its Biological Significance with Reference to Vitamin D., *Biochemical Jour.*, 1927, **21**, 85.

<sup>2</sup> Gardner, J. A. and Gainsborough, H.: Studies on the Cholesterol Content of Normal Human Plasma, *Biochem. Jour.*, 1927, **21**, 130.

Cholesterol is said to be present in the bile as a result of either one or both of two processes. It may be synthesized in the body, it may be ingested in various foods and excreted from the blood by the liver, or possibly it is formed in the biliary tract. McMaster<sup>1</sup> found that a diet rich in cholesterol increases both the total quantity and concentration of cholesterol in bile, independently of any elaboration by the gall bladder. There was no fixed relation between the quantity of bile and the amount of cholesterol excreted per day. Starvation decreased the quantity of cholesterol, but increased its concentration. Salmamon<sup>2</sup> confirms McMaster's findings by noting an increase in the cholesterol in the bile after feeding butter, eggs and brain. Arndt,<sup>3</sup> also, always found an increase of cholesterol in the blood after its administration by mouth, but did not always find a proportional increase in the bile.

There are other striking indications of the influence of diet. Fujimaki<sup>4</sup> observed that rats fed for a long period on a diet deficient in vitamin A develop in sequence bladder, renal and biliary calculi. The biliary calculi were cholesterol stones. Lack of vitamin B, or restriction of protein, did not seem to be concerned in such stone formation.

Further recent studies of the cholesterol content of blood and bile tend to prove the concept that systemic conditions are of great importance in cholesterol stone formation, rather than that all cholesterol in calculi arises from the wall of the bile tract as a result of inflammatory changes. Moehlig and Ainslee<sup>5</sup> conclude from clinical data that the pituitary gland, by regulating the suprarenal cortex and other mesodermal tissues, plays an important part in the diseases associated with abnormal cholesterol metabolism. On the other hand, Thomas<sup>6</sup> believes that an abnormally high cholesterolemia may influence the endocrine glands, such as the pituitary, and induce hypertension.

It has been suggested that factors controlling the cholesterol

<sup>1</sup> McMaster, P. D.: Studies on the Total Bile. VI. The Influence of Diet on the Output of Cholesterol in the Bile, *Jour. Exper. Med.*, 1924, **40**, 25.

<sup>2</sup> Salmamon, H.: Über die Einwirkung der Butter und die Cholesterinausscheidung in der Galle, *Arch. f. Verdauungskrankh.*, 1926, **39**, 46.

<sup>3</sup> Arndt, H. J.: Nahrungscholesterin, Blutscholesterin, Gallen-cholesterin, *Klin. Wchnschr.*, 1926, **5**, 1372.

<sup>4</sup> Fujimaki, Y.: Formation of Urinary and Bile-duct Calculi in Animals Fed on Experimental Rations, *Progress of Science of Nutrition in Japan*, League of Nations Health Organization, Geneva, 1926, p. 369.

<sup>5</sup> Moehlig, R. C. and Ainslee, H. B.: The Pituitary Gland and Cholesterol Metabolism, *Ann. Clin. Med.*, 1927, **5**, 772.

<sup>6</sup> Thomas, E.: Recherches Experimentales Touchant L'Influence de la Cholestérine sur le Développement de L'Hypertension Arterielle, *Arch. des Maladies du Cœur*, 1926, **19**, 641.



content of the blood may be an inherited character. Shope,<sup>1</sup> in his experiments with tuberculosis in guinea-pigs, found that it is probable that the cholesterol content of their blood serum is influenced by inherited factors. There is some slight clinical evidence that hereditary influences play a rôle in the formation of gall stones.

Another explanation offered for the presence of cholesterol in normal bile is that it arises from the mucous membranes lining the gall bladder and bile-ducts. Naunyn<sup>2</sup> believes that cholesterol, from which the calculi are largely formed, is not derived from the bile itself, but from the disintegration of the epithelial cells lining the gall bladder as a result of disturbed function of the gall bladder produced by inflammation. Bilirubin calcium acts as a cementing substance for the cholesterol. In contrast to this idea are the views of Aschoff and Bacmeister,<sup>3</sup> who hold that disturbances of cholesterol metabolism in the body are contributing factors in the formation of biliary calculi. They believe that solitary pure cholesterol stones may form independently of inflammation. These stones favor infection and inflammation of the gall bladder and as a result multiple calculi containing calcium may form. Aschoff<sup>4</sup> recently restated his opinion that hypercholesterolemia, stasis of bile, and gall bladder infection, are the associated factors in the formation of gall stones.

As has been noted in the chapter on Physiology of the Gall Bladder, it has been stated by Adami and Nicholls,<sup>5</sup> Herter<sup>6</sup> and others that the epithelial cells of the mucosa of the gall bladder can excrete cholesterol. They believe that at least part of the cholesterol found in the bile of the gall bladder is accounted for in this way.

Other workers are of the opinion that the cholesterol accumulation which may be demonstrated in the epithelial cells of the gall bladder wall are a result of the ability of the mucosa of the gall bladder to absorb cholesterol. Among those who adhere to this

<sup>1</sup> Shope, R. E.: Quantity of Cholesterol in Blood as Inherited Character: Relation to Resistance to Tuberculosis, *Jour. Exper. Med.*, 1927, **45**, 59.

<sup>2</sup> Naunyn, B.: *Klinik der Cholelithiasis*, Verlag von F. C. W. Vogel, Leipzig, 1892, translation by A. E. Garrod, New Sydenham Soc., 1896; *Die Cholelithiasis*, G. Fischer, Jena, 1921; *Die Gallensteine, ihre Entstehung und ihr Bau*, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1921, **33**, 1.

<sup>3</sup> Aschoff, L. and Bacmeister, A.: *Die Cholelithiasis*, Verlag von Gustav Fischer, Jena, 1909.

<sup>4</sup> Aschoff, Ludwig: *Lectures on Pathology*, Paul B. Hoeber, New York, 1924.

<sup>5</sup> Adami, J. G. and Nicholls, A. G.: *Principles of Pathology*, Lea & Febiger, Philadelphia, 1909.

<sup>6</sup> Herter, C. A.: The Etiology of Chemical Pathology of Gall Stones, *Trans. Congr. Am. Phys. and Surg.*, 1903, **6**, 158.

idea are Grigaut,<sup>1</sup> Dewey,<sup>2</sup> Meyer *et al.*,<sup>3</sup> Boyd,<sup>4</sup> Sweet<sup>5</sup> and Mentzer.<sup>6</sup> The work of Sweet is especially interesting. He found the total blood cholesterol to rise immediately after removal of the gall bladder, to fall to the normal level about forty days after operation, and below normal shortly afterward. The maximum rise of blood cholesterol after fat ingestion was found to occur normally in the sixth hour afterward, and not until the ninth hour afterward when the gall bladder had been removed previously.

There are many adherents of the hypercholesterol theory of Aschoff and Baemeister.<sup>7</sup> Rovsing<sup>8</sup> examined 530 cases of gall stones and found that 311 of them were sterile. He believes infection of the gall bladder in the presence of stones is always secondary to the presence of the stones. Wilensky,<sup>9</sup> Rothschild and Wilensky,<sup>10</sup> as well as Rovsing, believe that a saturation of the gall bladder bile with cholesterol will precipitate stones. Moynihan<sup>11</sup> also believes that an increased cholesterol content of the blood and a preceding infection of the biliary tract are the two chief factors in the causation of gall stones. He finds the normal cholesterol content of the blood to be from 0.133 per cent to 0.160 per cent. In a study of 101 cases of gall stones, 66.4 per cent of the patients being women, there were 65 per cent of the cases which showed a hypercholesterolemia and 23 per cent a high normal content. Mentzer<sup>12</sup> compared the blood cholesterol of patients with gall-bladder disease with patients having a normal gall bladder at operation and found a relative increase in the blood lipoids of the former. The blood cholesterol was determined by Fowweather and Collinson<sup>13</sup> in 75

<sup>1</sup> Grigaut, A.: *Le Cycle de la Cholesterinemie*, Paris, 1913.

<sup>2</sup> Dewey, K.: *Experimental Hypercholesterolemia*, Arch. Int. Med., 1916, **17**, 785.

<sup>3</sup> Meyer, K. F., Neilson, N. M. and Feusier, M. L.: *Mechanism of Gall Bladder Infections in Laboratory Animals*, Jour. Infec. Dis., 1921, **28**, 456, 510.

<sup>4</sup> Boyd, William: *Studies in Gall Bladder Pathology*, British Jour. Surg., 1923, **10**, 337.

<sup>5</sup> Sweet, J. E.: *The Gall Bladder: Its Past, Present and Future*, Int. Clin., 1924, **1**, 187.

<sup>6</sup> Mentzer, S. H.: *Cholesterosis of the Gall Bladder*, Am. Jour. Path., 1925, **1**, 383.

<sup>7</sup> Aschoff, L. and Baemeister, A.: *Die Cholelithiasis*, Verlag von Gustav Fischer Jena, 1909.

<sup>8</sup> Rovsing, T.: *Gall Stones, Cause, Not Result of Infection*, Acta Chir. Scandinav., 1923, **56**, 103, 207.

<sup>9</sup> Wilensky, A. D.: *Hypercholesterolemia*, Surg., Gynec. and Obst., 1924, **38**, 163.

<sup>10</sup> Rothschild, M. A. and Wilensky, A. D.: *Studies in Cholelithiasis: I. The Disturbance of the Cholesterin Metabolism as a Factor in Gall-stone Formation*, Am. Jour. Med. Sci., 1918, **156**, 239; II. *The Clinical Relationships of the Cholesterinemia to the Pathological Process*, Ibid., 1918, **156**, 404.

<sup>11</sup> Moynihan, Sir Berkeley: *Some Aspects of Cholelithiasis*, British Med. Jour., 1925, **i**, 393.

<sup>12</sup> Mentzer, S. H.: *The Pathogenesis of Biliary Calculi*, Arch. Surg., 1927, **14**, 14.

<sup>13</sup> Fowweather, F. S. and Collinson G. A.: *Chemical Changes Associated with Gall Stones: Relation between Gall Stones and Hypocholesterolemia*, British Jour. Surg., 1927, **14**, 583.

cases of gall stones. Thirty-five (46.7 per cent) showed definitely increased values and 8 (10.9 per cent) showed high normal values. There were low normal values in only 4 cases.

The association of pregnancy with gall-bladder disease has been mentioned. It is of significance in that a hypercholesterolemia has been found by a number of workers in pregnancy and for a short period afterward. Furthermore, it is common knowledge that a very high percentage of women having gall stones have borne children and that frequently there are symptoms of gall-bladder disease in the latter months of pregnancy. Aschoff<sup>1</sup> suggested that women who after delivery show a hypercholesterolemia and do not excrete some of their fats in their milk by suckling their offspring are likely to develop gall stones. These facts, together with the possible tendency toward stasis of the bile in the tract during pregnancy as a result of a combination of factors, make it probable that there is a direct association of pregnancy and gall-bladder disease.

However, it is probable that cholesterol, or an excess of it, is not necessary for the production of all types of calculi. Certainly some of the calcium stones contain practically no cholesterol. Campbell,<sup>2</sup> furthermore, in contrast to Moynihan,<sup>3</sup> found the amount of cholesterol in the blood of patients with cholecystitis and cholelithiasis to be within normal limits, provided the subject is not jaundiced. Therefore, the determination of the cholesterol content of the blood was of no help to him in the diagnosis of gall stones. His findings did not exclude, though they did not support, the theory that the formation of gall stones is caused by a hypercholesterolemia of the blood and bile.

A high cholesterol content of the blood may be due to a diminished excretion. The amount is usually increased in obstructive jaundice. Chabrol, Bernard and Gambillard<sup>4</sup> attribute the hypercholesterolemia in gall-stone disease largely to an insufficient drainage of the biliary tract. Stern and Suchantke<sup>5</sup> found that experimental injury of the parenchyma of the liver by drugs leads to an increase of the cholesterol content of the blood.

<sup>1</sup> Aschoff, Ludwig: Lectures on Pathology, Paul B. Hoeber, Inc., New York, 1924.

<sup>2</sup> Campbell, J. M. H.: Cholesterol in the Blood in Cases of Gall Stones, *Quart. Jour. Med.*, 1924, **18**, 123.

<sup>3</sup> Moynihan, Sir Berkeley: Some Aspects of Cholelithiasis, *British Med. Jour.*, 1925, **i**, 393.

<sup>4</sup> Chabrol, E., Bernard, H. and Gambillard: Recherches sur L'Elimination de la Cholesterine par le Foie; Application a L'Étude de la Lithiase Biliaire, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1924, **48**, 1145.

<sup>5</sup> Stern, R. and Suchantke, G.: Ueber die klinische Bedeutung des Cholesterins in der Galle und im Blustrom. III. Das Gleichgewicht von Cholesterin und Cholesterin-ester in Blutserum bei gestörter Leberfunktion, *Arch. f. exp. Path. u. Pharmak.*, 1926, **115**, 221.

**Lichtwitz's Theory.**—According to Lichtwitz,<sup>1</sup> bile is a colloid held in suspension by ions with negative charges. Alteration of these charges by changes in the acid-base reaction of the bile results in a precipitation of cholesterol. The bile salts probably hold cholesterol in suspension in the bile. A change in these salts, resulting in a variation of the acidity of the bile or a change in the cholesterol content, could disturb the equilibrium of the suspension of the cholesterol ions, with possible precipitation of cholesterol. The cholesterol content of bile is known to vary and it is possible that the content of bile salts may vary with diet and with various states of the liver.

This theory is somewhat substantiated by an observation of Oliver<sup>2</sup> that bile placed in a test-tube, taken from a gall bladder in which stones had formed, would precipitate in layers. Normal bile will not do this. Rous, McMaster and Drury<sup>3</sup> found that if acid is added to the bile it will not precipitate. They also concluded that the absence of stones in the normal gall bladder is because of the changed reaction of the bile produced by the gall bladder. This alteration permits the bile to be stored safely.

**Theory of "Protective Colloids."**—In his text-book on physical chemistry, Findlay<sup>4</sup> discusses the part that physical chemistry may play in the formation of biliary calculi. It is known that emulsoid colloids exercise a protective action over the suspensoids and render them more stable. The formation of gall stones is said to be produced by a reduction in the amount of protective colloids in the bile brought about by abnormal conditions. The protective colloids, which in the normal bile are the bile salts, albuminoids, and other proteins, tend to keep the sparingly soluble substances in a colloidal suspension. A separation of the sparingly soluble substances takes place when the protective colloids are destroyed.<sup>5</sup>

<sup>1</sup> Lichtwitz, L.: Experimentelle Untersuchungen über die Bildung von Niederschlägen in der Galle, Deutsch. Arch. f. klin. Med., 1907, **92**, 100.

<sup>2</sup> Oliver, S. F.: Etiology of Gall Stones, Jour. Lab. and Clin. Med., 1923, **8**, 242.

<sup>3</sup> Rous, P., McMaster, P. D. and Drury, D. R.: The Genesis of Gall Stones in the Dog, Proc. Soc. Exper. Biol. and Med., 1923, **20**, 6; Observations on Some Causes of Gall-stone Formation: I. Experimental Cholelithiasis in the Absence of Stasis, Infection and Gall-bladder Influences, Jour. Exper. Med., 1924, **39**, 77; II. On Certain Special Nuclei of Deposition in Experimental Cholelithiasis, Ibid., 1924, **39**, 97; III. The Relation of the Reaction of the Bile to Experimental Cholelithiasis, Ibid. 1924, **39**, 403.

<sup>4</sup> Findlay, A.: Physical Chemistry for Students of Medicine, Longmans, Green & Co., New York, 1924, p. 197.

<sup>5</sup> In a recent note F. M. Harrison and W. H. Barber (Effect of Living Gall Bladder on Human Biliary Calculi, Proc. Soc. Exper. Biol. and Med., 1927, **25**, 226) have recorded the very interesting observation that human gall stones diminish in size and actually disappear when placed in the gall bladders of living dogs. In 8 experiments, after sixty days, the stones had diminished in size in 3 and had disappeared in 5.



### MIGRATION OF BILIARY CALCULI.

Biliary calculi may be found in any portion of the biliary tract, and in almost any number. They are found most frequently in the gall bladder, but not infrequently in the common and hepatic ducts. Stones found in the cystic or common duct may have found their way there from the gall bladder or the intra-hepatic ducts. A calculus may produce a diverticulum in the wall of the gall bladder or the common duct. Occasionally, when they lie in the intra-mural portion of the common duct, they may produce a diverticulum of that portion of the duodenum.

Small stones formed in the intra-hepatic ducts may find their way into the gall bladder by reason of the normal ebb and flow of bile and act as nuclei for the formation of larger gall stones. Stones pass from the fundus of the gall bladder through the cystic and common ducts into the duodenum.

Sweet<sup>1</sup> suggests that multiple facettted gall stones found in the gall bladder have their origin in the many pockets of the cystic duct at the valves of Heister. He believes soft masses of various bile constituents lodge in these pockets and conform to the shape of the cavity. Chemical changes transform the soft masses into stones which block the cystic duct. Internal duct pressure, which causes a dilatation of the common duct after cholecystectomy if the sphincter of Oddi is competent, forces the newly-formed stone from the cystic duct into the gall bladder. The process repeats itself until there may be a collection of stones varying in size and shape according to the character of the pockets in the cystic duct.

The period of migration of stones is most important clinically. The location, size, shape and consistency of the stone or stones are important factors determining their progress in their passage through the ducts. The natural tendency of a stone seems to be to move with the bile into the duodenum. Small calculi may pass freely through the ampulla of Vater into the duodenum, while larger ones excite definite signs and symptoms. Soft, easily molded stones would seem to move more readily than large, firm ones which must produce a dilatation of the ducts as they proceed in their passage. The most difficult sites of progress in the extrahepatic ducts are through the cystic duct and the duodenal ampulla.

The forces concerned in the expulsion of a stone from the bile-ducts are not entirely understood. An important factor may be

<sup>1</sup> Sweet, J. E.: The Importance to Surgery of the Cystic Duct, *Am. Jour. Surg.*, 1927, New Series, 3, 274.

the contraction of the muscle fibers in the walls of the gall bladder and bile-ducts, but this is not entirely certain. A muscular contraction of the gall bladder may exert its force directly on the stone or stones or its force may be transmitted through bile to increase the pressure behind a stone in the cystic or common ducts. Even without muscular contractions the pressure in the gall bladder from distention as a result of blocking of the cystic duct may be very considerable, and may conceivably play a more important rôle than muscular contractions. The common duct doubtless has an independent power of contraction which may force stones forward. Waves of pressure changes in the common duct which have been interpreted as being due to contractions of the musculature, have been demonstrated by Copher and others.

Particularly during gall-stone colic, indirect pressure is made to some degree on the gall bladder and ducts by the voluntary and involuntary movements of the diaphragm and abdominal muscles. The combination of these propelling forces may dilate the ducts behind the obstructing stone. The stone proceeds down the lumen of the tract as it overcomes the resistance which is produced by over-distention and spasm of the wall of the duct.

A slight addition to the propelling forces concerned with the movement of gall stones is made by pressure under which bile is secreted by the liver.

The factors which initiate movement of gall stones are of great interest, even if in general they are obscure. It is probable that the migration of stones may be initiated by the normal contractions of the musculature of the gall bladder and common duct incident to digestive processes. Forcible contraction of the abdominal muscles may dislodge a hitherto quiescent stone. Patients frequently date the onset of their biliary colic from stooping, jolting of the body by a suddenly applied force, exercise, etc.

Stones often eventually escape through the common duct into the duodenum. The passage of the stone down the duct is accomplished in varying periods of time. However, it may become permanently impacted with consequent signs and symptoms of obstruction to the flow of bile. Continued impaction of a stone may result in ulceration of the wall of the biliary passages. Rupture of the wall of the bile-duct or gall bladder may follow ulceration. Unless protecting adhesions have been formed about the site of perforation, the contents of the biliary tract may escape into the peritoneal cavity, giving rise to a local or general peritonitis.

If the inflammatory process remains localized by adhesions and

neighboring organs, false passages or biliary fistulæ may be formed between the biliary tract and adherent organs or the external surface of the body. Biliary fistulæ occur in several forms. The most common varieties occur between the gall bladder and the duodenum and between the gall bladder and the colon. Less common varieties are fistulæ between the biliary passages themselves, between the biliary tract and the stomach, the genito-urinary tract and lungs. Many other rarer forms of biliary fistulæ have been reported. (See page 225.)

Once within the intestinal tract, the majority of stones escape from the body without difficulty. They may be vomited or, more usually, are passed in the stools. The passage of a stone from the rectum has occasionally been the first indication to the patient that he harbored stones. Stones as large as 4 by 9 cm. have been reported to have been passed per rectum without any very great difficulty.

A biliary calculus may be too large to pass through the small intestine or through the ileo-cecal valve and so produce an intestinal obstruction. The impaction of calculi in the lumen of the intestine occurs most frequently in women during their fifth and sixth decade. The symptoms of intestinal obstruction from gall stones are similar to those due to other causes. Impacted gall stones in the intestine have been known to perforate the intestine and to produce stricture of the intestine.

#### **CHOLELITHIASIS AND CANCER OF THE BILIARY TRACT.**

Cancer of the gall bladder is frequently associated with cholelithiasis. There is some question as to which process is primary. It has been held that stones may act as a stimulus for a new growth of the bile passages, while others believe that a new growth of the gall bladder or ducts may predispose or actively excite stone formation. Calculi are probably more frequently associated with cancer of the gall bladder than with cancer of the bile-ducts. It is probable, though, new growths frequently develop after calculi have passed from the ducts. The subject of carcinoma and its relation to gall stones will be more fully discussed in Chapters V and VI.

## CHAPTER V.

### SYMPTOMS AND CLINICAL DIAGNOSIS OF DISEASES OF THE GALL BLADDER.

#### CHOLECYSTITIS.

INFLAMMATION of the gall bladder reveals itself in many forms. The clinical picture, therefore, of necessity will be likewise varied. Formerly the chief emphasis in text-books of medicine was placed on the more severe and the late manifestations of inflammation. As in other conditions, however, an effort should be made to establish a diagnosis in the early and relatively mild cases in order to forestall as much as possible the late effects. These late effects are not of so much importance as regards the gall bladder itself, but they become important because other organs are likely to be seriously damaged by the infection in the gall bladder. These organs are particularly the liver, the pancreas and the heart.

It is customary in most discussions of the clinical features of cholecystitis to subdivide the condition into a number of others, such as catarrhal cholecystitis, suppurative cholecystitis, phlegmonous cholecystitis, empyema of the gall bladder, etc. It seems to us, however, wiser to consider this topic under such general heads as (1) acute cholecystitis, and (2) chronic cholecystitis.

**Acute Cholecystitis.**—Of 848 cases of disease of the gall bladder in the Barnes Hospital, only 7.6 per cent were of acute cholecystitis.

As in other acute infections the onset is usually sudden, sometimes with a chill. It occasionally begins during the course of some other disease, as for example, typhoid fever, acute tonsillitis, etc. Evidences of peritonitis supervene early. These consist of pain, chiefly in the right upper quadrant of the abdomen, muscular rigidity and tenderness more pronounced in that region, vomiting, leukocytosis and fever. The pain is usually of a continuous aching character and very severe. Often, however, it is cramp-like with severe paroxysms, especially if stones are present. The pain is often referred to the back, particularly to the region of the angle of the right scapula and to the lower dorsal spine. Cope<sup>1</sup> has made a

<sup>1</sup> Cope, Z.: A Clinical Study of Phrenic Shoulder Pain; with Special Bearing on the Diagnosis of Acute Abdominal Disease, *British Jour. Surg.*, 1922-1923, **10**, 192.



special study of the shoulder pain in cases of acute diseases of the biliary tract. He deplors the common mistake of thinking that the pain of biliary tract disease is frequently referred to the top of the right shoulder, instead of under the right scapula. He states, moreover, that it is easy to demonstrate that: (1) Gall stones and gall-bladder disease are less commonly the cause of phrenic shoulder pain than are perforated pyloric or duodenal ulcer; (2) neither cholecystitis nor impaction of a stone in the cystic duct causes pain on the top of the right shoulder unless there is accompanying local peritonitis; (3) a stone impacted in the common duct does not cause pain on the top of the shoulder until congestion and edema of the adjacent parts result. The pain when referred to the top of the shoulder is in consequence of an irritation of the terminations of the phrenic nerve. It is felt over the areas of skin supplied by the same spinal segments which give origin to the phrenic nerve. The sensory distribution areas of the third, fourth and fifth cervical segments are the parts involved, though of these the fourth segment is by far the most important. Roughly speaking, the pain is felt within the areas supplied by the descending cutaneous branches of the third and fourth cervical nerves. This pain must be distinguished from the infrascapular segmental pain commonly felt in gall-stone disease and in some gastric conditions. Ordinarily the pain in acute cholecystitis begins to subside in about twenty-four or forty-eight hours, and in a typical case after about a week or ten days the symptoms are gone. Usually the chills are not severe, and the fever is not high (above 102° F.) unless there is a fairly extensive involvement of the liver by the inflammatory process. In a case of acute cholecystitis uncomplicated by stones, jaundice is ordinarily not a conspicuous feature. The occurrence of jaundice, following the symptoms given above, speaks for an obstruction of hepatic bile, which may be due either to stones in the hepatic or common ducts or to an inflammatory obstruction of intra-hepatic ducts from edema, infiltration with leukocytes, etc. It was shown by one of us (Graham) that apparently in all cases of cholecystitis there is an associated hepatitis which is characterized by an inflammation around the intra-hepatic bile-ducts (pericholangitis). Naturally in some cases this is of a more severe grade than in others, and consequently, as might be expected, the severity of the jaundice due to this cause in different cases will be variable. The leukocytosis is usually not excessive, about 12,000 to 18,000. Respiration is painful, and for that reason it may be restricted on the right side and jerky.

Obstruction of the cystic duct by a stone gives rise to a distention and an enlargement of the gall bladder. In acute obstructive inflammations the organ may be filled with pus, a condition known as *empyema* of the gall bladder. It is a noteworthy fact, however, that even in such cases the mucous membrane of the gall bladder is not destroyed. If jaundice is present it is only slight in amount, and it is due in such cases to an inflammatory swelling within the liver which closes off some of the finer bile-ducts. When a stone is present in the cystic duct the pain, instead of being more or less continuous, may be paroxysmal and very severe during the paroxysms. If the obstruction to the duct is relieved either by the passage of the stone or by its falling into the gall bladder the pain will cease abruptly.

On examination of a patient during an attack of acute cholecystitis one often finds evidence of some enlargement of the liver. If the rigidity of the abdominal muscles is not too great the edge of the liver can often be felt, and it is found to be abnormally tender not only in the region of the gall bladder but often also along the edge of the left lobe. Sometimes also an enlarged tense gall bladder can be felt through a thin abdominal wall. Tenderness is often elicited by pressure over the eleventh or twelfth dorsal vertebræ.

An attack of acute cholecystitis almost invariably subsides spontaneously. It is extremely rare for perforation of the gall bladder to occur except in the cases of acute typhoidal cholecystitis. (See Chapter III.) In this respect the condition is much less dangerous, in itself, than acute appendicitis. When perforation does occur the symptoms and signs of peritonitis become more and more progressive unless the site of the perforation becomes sealed by a walling off by the omentum or other abdominal structures. There is, however, a curious rare condition in which bile is found in the free peritoneal cavity without any evidence of perforation of the gall bladder or of the bile-ducts. By some this condition has been supposed to follow the perforation of hernial protrusions of the mucous membrane through the wall of the gall bladder, the so-called Luschka's canals. Johansson<sup>1</sup> in 1912 collected 5 cases. Since then additional cases have been reported by Leriche<sup>2</sup> who found 1500 cc. of bile in the abdominal cavity despite the fact that the gall bladder was distended without any sign of perforation, and by

<sup>1</sup> Johansson, S.: Contribution à l'Étude de la perihepatite bilieuse avec épanchement biliaire dans le péritoine sans perforation de l'appareil biliaire, *Rev. de Chir.* 1912, **46**, 392.

<sup>2</sup> Leriche, R.: De la transsudation biliaire à travers la vésicule non perforée, *Presse méd.*, 1923, **31**, 252.

Marinacci.<sup>1</sup> A study of the effect of the escape of sterile bile into the peritoneal cavity has been made by Wangenstein<sup>2</sup> who, after an extensive review of the literature and a number of animal experiments, concludes that the leakage of sterile bile in large amounts into the peritoneal cavity is fatal unless it is removed. He states that there is no instance of recovery after the subcutaneous rupture of the normal bile passages unless the bile has been removed by operation or by puncture. The cause of death he considers to be cholemia.

The diagnosis of acute cholecystitis is usually easy in a typical case. A sudden severe attack of pain in the right upper quadrant with vomiting, tenderness and muscular rigidity in this region almost always speaks for an acute inflammation of the gall bladder. However, almost any other acute intra-abdominal inflammatory condition may, at times, begin with such symptoms. In many cases of acute cholecystitis a diagnosis of acute appendicitis has been made, and the patients have been operated upon under such an erroneous opinion. Perforation of a peptic ulcer may give symptoms closely simulating those of an acute inflammation of the gall bladder. The picture is often of a particularly puzzling nature because, if the condition is one of an acute exacerbation of a chronic cholecystitis, the history of chronic dyspepsia may be very suggestive of a peptic ulcer. The seriousness of a possible mistake is of course greater if an acute appendicitis or a perforated peptic ulcer is erroneously considered to be an acute inflammation of the gall bladder than *vice versa* because the postponement of operation in the former contingencies might be disastrous. In peritonitis from appendicitis or from a perforated ulcer the symptoms are usually more severe, the location of maximal tenderness is different, and, especially in the case of a differentiation from appendicitis, the age of the patient is important. Appendicitis is most frequent in young adults, while cholecystitis is most common during middle age, in women, and in those with a tendency to obesity. Acute pyelitis and renal colic are both sometimes confused with acute cholecystitis. An examination of the urine for pus or blood is helpful in ruling out these conditions.

It is of the greatest importance also to realize that serious cardiac conditions, such as coronary thrombosis and infarction or angina pectoris, may give rise to symptoms very similar to those of acute cholecystitis. Even tenderness and rigidity in the right upper quad-

<sup>1</sup> Marinacci, S.: Coleperitoneo con integrità apparente delle vie biliari, *IL Policlinico* (Sez. Prat.), 1925, **32**, 1422.

<sup>2</sup> Wangenstein, O. H.: On the Significance of the Escape of Sterile Bile into the Peritoneal Cavity, *Ann. Surg.*, 1926, **84**, 691.

rant may be present in the former because of a sudden engorgement and swelling of the liver with blood. It is a strange fact that the text-books give almost no mention of the possibility of confusing cardiac conditions with acute surgical abdominal conditions, although it is a fairly frequent mistake. Patients with coronary infarcts have been operated upon under the misconception that they were suffering from surgical abdominal conditions, and often with disastrous results. Levine and Tranter<sup>1</sup> have discussed this matter, with the report of 2 cases. A much more extensive presentation of this question, however, is that of Faulkner, Marble and White<sup>2</sup> who made a comparative study of 30 consecutive cases of occlusion of a coronary artery of the heart found at operation and 30 consecutive cases of cholelithiasis confirmed at operation. In their cases the location of pain was as follows:

Position of pain.	Coronary occlusion.	Cholelithiasis.
Precordial . . . . .	2	0
Substernal . . . . .	2	0
Chest . . . . .	1	0
Both precordial and epigastric . . . . .	2	0
Epigastric . . . . .	5	15
Lower abdomen . . . . .	2	0
Diffusely over abdomen . . . . .	1	0
Right upper quadrant . . . . .	0	9
Right upper quadrant and epigastrium . . . . .	0	1
Lower right thorax . . . . .	0	2
Angle of right scapula . . . . .	0	1
Left breast . . . . .	0	1
Both flanks . . . . .	0	1

Of equal interest is their analysis of the association of other symptoms with the attack of pain which is as follows:

	Coronary occlusion.	Cholelithiasis.
Nausea . . . . .	5	12
Vomiting . . . . .	7	16
Palpitation . . . . .	3	0
Dyspnea . . . . .	17	0
Syncope . . . . .	6	0
Faintness . . . . .	5	0
Vertigo . . . . .	3	0
Weakness . . . . .	4	2
Tenderness in right upper quadrant . . . . .	5	23

Pneumonia and pleurisy on the right side can also produce symptoms which can be easily confused with acute cholecystitis. A careful examination of the chest, however, will usually clear the confusion. Lead colic and the abdominal crises of tabes dorsalis

<sup>1</sup> Levine, S. A. and Tranter, C. L.: Infarction of the Heart Simulating Acute Surgical Abdominal Conditions, *Am. Jour. Med. Sci.*, 1918, **155**, 57.

<sup>2</sup> Faulkner, J. M., Marble, H. C. and White, P. D.: The Differential Diagnosis of Coronary Occlusion and of Cholelithiasis, *Jour. Am. Med. Assn.*, 1924, **83**, 2080.



also may closely simulate an acute inflammation of the gall bladder. The presence of a Riedel's lobe may serve to make the picture more confusing because it may be erroneously taken for an enlarged gall bladder. On the other hand, since chronic cholecystitis is a frequent accompaniment of a Riedel's lobe, the presumptive evidence is strong that acute inflammatory symptoms and signs in the right upper quadrant have their origin in the gall bladder if such a lobe can be made out on physical examination. The value of an ordinary roentgen-ray examination in a case of acute cholecystitis is slight, but roentgen-ray examination by cholecystography will be found to be of great value, although the examination should be withheld until after the symptoms have begun to subside. Ordinary roentgen-ray examination, however, will be helpful in ruling out a renal colic from stone and also, occasionally, in some cases in which a pneumoperitoneum from a perforated peptic ulcer may be demonstrated. (Copher.<sup>1</sup>) The question of the roentgen-ray examination of cases of acute cholecystitis, both by ordinary means and by cholecystography, is fully discussed in the separate sections dealing with that subject. Lyon's<sup>2</sup> method of drainage of the biliary tract by means of a duodenal tube has been found helpful by some in establishing a diagnosis in these cases. This procedure will be more extensively discussed later.

**Complications.**—An important complication of acute cholecystitis is acute hemorrhagic pancreatitis, or acute pancreatic necrosis. This complication is most likely to occur if calculi are present. Opie<sup>3</sup> considered that at least some of these cases were due to a blocking of the ampulla of Vater by a stone with the result that bile was forced up the pancreatic duct into the pancreas. Archibald<sup>4</sup> has felt that the same mechanism could occur, even without the presence of a stone, as the result of contraction of the common-duct sphincter. Jones<sup>5</sup> has critically discussed the whole question of pathogenesis. In the cases associated with acute pancreatitis the patient usually is profoundly prostrated, and the symptoms of peritonitis are both generalized and extreme. Tenderness, however,

<sup>1</sup> Copher, G. H.: Demonstration of Spontaneous Pneumoperitoneum by the Roentgen Ray; an Aid in the Diagnosis of Acute Perforating Peptic Ulcer, *Jour. Am. Med. Assn.*, 1924, **82**, 781.

<sup>2</sup> Lyon, B. B. V.: *Non-surgical Drainage of the Gall Tract*, 1923, Philadelphia, Lea & Febiger.

<sup>3</sup> Opie, E. L.: *Disease of the Pancreas, its Cause and Nature*, 2d ed., 1910 Philadelphia, J. B. Lippincott, Company.

<sup>4</sup> Archibald, E.: The Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common-duct Sphincter, *Surg., Gynec. and Obst.*, 1919, **28**, 529.

<sup>5</sup> Jones, D. F.: Acute Pancreatitis, *Surg. Clin. of North America*, 1922, **2**, 1125.

is most pronounced in the mid-epigastrium. Attacks of acute arthritis or acute exacerbations of chronic arthritis not infrequently occur during or shortly after an attack of acute inflammation of the gall bladder. The myocardium may be seriously damaged by acute cholecystitis, and a patient who already has a chronic myocarditis may show a marked arrhythmia and even evidences of decompensation as a result of an attack of acute inflammation of the gall bladder. Also patients with toxic goiters may manifest even alarming exacerbations of their conditions during or shortly after an attack of acute cholecystitis.

**Chronic Cholecystitis.**—Chronic disturbances of the gall bladder constitute one of the most frequent ailments of adult humanity. There is no more interesting chapter in the history of medicine than the gradual development of the idea that this organ is accountable for much of the dyspepsia, much of the partial invalidism and even a fair proportion of the cancer of the world. This is in striking contrast to the older view which regarded as cases of chronic cholecystitis only those in which there were recurrent attacks of biliary colic. This accomplishment must be laid almost entirely to the credit of the clinicians, as the pathologists have been of scant help. Even today many of them disregard at the postmortem examination anything but the most gross lesions of the gall bladder, and those chiefly associated with calculi. As evidence, however, of the newer clinical conceptions of the consequences of chronic disturbances of the gall bladder, it may be stated that cholecystitis is recognized by many to be the most frequent organic cause of dyspepsia. Blackford and Dwyer<sup>1</sup> found in a series of 1650 patients with gastric symptoms that the approximate relative frequency of abdominal organic disease causing dyspepsia was: Gastric ulcer, 1; gastric carcinoma, 2; "reflex" appendicitis, 4; duodenal ulcer, 6; gall-bladder disease, 12. Eusterman<sup>2</sup> from a study made at the Mayo Clinic states that of the patients with gastric symptoms there are 60 per cent more cases associated with a diseased gall bladder than with a peptic ulcer.

Of the chronic disturbances of the gall bladder which are generally known as cholecystitis, all are not definitely inflammatory processes. The gall bladder which presents on its mucosa small yellowish granules of lipid material which MacCarty<sup>3</sup> has called the "strawberry"

<sup>1</sup> Blackford, J. M. and Dwyer, M. F.: Gastric Symptoms with Particular Reference to Gall-bladder Disease, *Jour. Am. Med. Assn.*, 1924, **83**, 412.

<sup>2</sup> Eusterman, G. B.: Discussion, *Jour. Am. Med. Assn.*, 1924, **83**, 415.

<sup>3</sup> MacCarty, W. C.: The Frequency of "Strawberry" Gall Bladders, *Ann. Surg.*, 1919, **69**, 131.

gall bladder, a condition designated by some as cholesterosis of the gall bladder, does not always present the true characteristics of inflammation. Nevertheless such a gall bladder may cause symptoms analogous to those produced by a true chronic cholecystitis. It would be better perhaps to designate the condition presented by a strawberry gall bladder as a cholecystopathy instead of a cholecystitis, as someone has already suggested. This condition is very poorly understood at the present time. It perhaps represents merely a functional disturbance of the organ, and until we have a more accurate knowledge of its functions it will be difficult to understand this lipid infiltration of the mucosa. There is an increasing tendency at the present time to consider the gall bladder as in some way concerned with the metabolism of cholesterol. These yellowish deposits have been found to be cholesterol esters. It is not yet certain, however, whether they signify that cholesterol is being withdrawn from the bile or that they are deposited from the blood stream. It is interesting in this connection that as early as 1857 Virchow, because of having recognized these granules as lipoidal in nature, thought that a part of the fats of the bile is reabsorbed by the mucosa of the gall bladder. Moreover, he expressed the opinion that "the gall bladder is not a mere reservoir but has a further function, for through it fats find an intermediate passage way back into the circulation."

The symptoms of chronic cholecystitis are extremely varied. In some cases there are recurring attacks of severe biliary colic, at times followed by jaundice. These are the cases in which stones are likely to be present. Of 380 gall bladders removed at the Barnes Hospital, 209 or 55 per cent contained stones. In other cases there are spells of vague soreness or discomfort in the upper abdomen, a little more marked on the right side. In still others there may be only dyspeptic symptoms or disturbances in other parts of the body, as for example the joints, related to the gall bladder only as it is a focus of infection. Again, the symptoms may be referable largely to pericholecystic adhesions to other organs. Finally they may be due to a carcinoma. In a considerable number of cases chronic cholecystitis is associated with a chronic appendicitis and with a chronic peptic ulcer.

It is chiefly a disease of middle age. However, there is a constantly increasing amount of evidence that cholecystitis and even cholelithiasis is by no means rare in childhood. It seems not improbable that many cases of chronic cholecystitis seen in the adult have had their origins in early life. The progress of most cases of chole-

cystitis is notoriously slow. Alvarez<sup>1</sup> found in a study of 60 cases in which operation was performed that the average duration of symptoms was nineteen years. He also believes from his study that many cases begin in childhood. Our own experience with cholecystography has revealed a surprisingly large number of diseased gall bladders in young children. Collections of cases, both with and without stones, have been reported by Khautz,<sup>2</sup> Eisendrath,<sup>3</sup> Matthews<sup>4</sup> and by Reid and Montgomery.<sup>5</sup> Cholesterin calculi have been found even in the newly-born.

The incidence of cholecystitis is much higher in women than in men (about 2 to 1), and strongly predisposing factors are multiple pregnancies and obesity. The adage of "female, fat and forty" as suggestive of chronic cholecystitis has much truth behind it. There is so high an incidence of chronic disturbance of the gall bladder in women who have gone through multiple pregnancies that probably few who have borne three or more children have normal gall bladders. No entirely satisfactory explanation has yet been offered of this striking relationship between pregnancy and cholecystic disease.

The association of dyspepsia with chronic cholecystitis has never been adequately explained. There is a considerable divergence of views concerning the gastric acidity in cases of chronic inflammation of the gall bladder. At any rate, the lack of uniformity in this regard would indicate that the amount of hydrochloric acid in the stomach has little to do with the presence or absence of the dyspeptic symptoms in these cases. Bonar<sup>6</sup> found 49 per cent to have achlorhydria and 23 per cent to have hyperchlorhydria. On the other hand, Griffiths<sup>7</sup> found 90 per cent to have hyperchlorhydria. Piersol and Bockus<sup>8</sup> in a study of 40 cases of cholecystitis found the pancreatic enzymes to be diminished in 85 per cent of the cases. In spite of the frequency of dyspepsia in association with cholecystitis, however,

<sup>1</sup> Alvarez, W. C. (and others): Gall-bladder Infections, Jour. Am. Med. Assn., 1923, **81**, 974.

<sup>2</sup> Khautz, A.: Cholelithiasis und Cholecystitis im Kindesalter und ihre Behandlung, Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1913, **16**, 546.

<sup>3</sup> Eisendrath, D. N.: Gall Bladder in Infancy and Childhood, Ann. Surg., 1917, **66**, 557.

<sup>4</sup> Matthews, F. S.: Gall Stones in the Young, Ann. Surg., 1914, **59**, 781.

<sup>5</sup> Reid, M. R. and Montgomery, J. C.: Acute Cholecystitis in Children as a Complication of Typhoid Fever, Bull. Johns Hopkins Hosp., 1920, **31**, 7.

<sup>6</sup> Bonar, T. G.: Gastric Secretion in Appendicitis and Cholelithiasis, Guy's Hosp. Rep., 1922, **72**, 400.

<sup>7</sup> Griffiths, H. E.: Relationships of Diseases of Gall Bladder to Secretory Functions of Stomach and Pancreas, Lancet, 1924, ii, 203.

<sup>8</sup> Piersol, G. M. and Bockus, H. L.: Pancreatic Enzymes in Cholecystitis, Arch. Int. Med., 1925, **35**, 204.



it is wise not to perform operations on the gall bladder merely because the patient complains of an otherwise unexplained dyspepsia. Scrimger<sup>1</sup> offers theories of the production of gastric symptoms on the basis of nerve distribution. A stone impacted in the cystic duct, for example, may give rise to pain with rigidity of the right rectus muscle through its sympathetic connection with the fifth to the ninth dorsal segments. At the same time vagus reflexes are set up which are distributed widely as spasm of muscle in the stomach and intestine with increased secretion. In the less acute conditions, the vagus reflexes may predominate, and in the intervals there may be disturbed function of the stomach or intestine, eructations of gas, hypermotility, hyperacidity, and constipation.

An interesting analysis of symptoms in 200 cases of cholecystitis, both with and without stones, proven by operation has been made by Millet.<sup>2</sup> In this group the average duration of symptoms was five and three-quarters years. Of the series 162 cases were chronic, 36 acute, and 2 were carcinomas.

SYMPTOMS.		Per cent.
Pain in right upper quadrant . . . . .		89
Nausea or vomiting or both . . . . .		48
Indigestion with flatulence . . . . .		37
Pain referred to shoulder . . . . .		35
Jaundice . . . . .		14
Constipation . . . . .		13
Loss of weight . . . . .		11
Chills or fever or both . . . . .		7

Jaundice, which was formerly regarded as a frequent symptom of cholecystitis, and indeed is still regarded today by many practitioners as almost a necessary one upon which to make a diagnosis, is seen from the above table to be uncommon and to occur in only 14 per cent of the cases. This incidence corresponds about with our own experience. The great importance of pain in the right upper quadrant is seen in its incidence of 89 per cent, but of almost equal frequency are the gastric symptoms, present in 85 per cent of the cases.

In Blalock's<sup>3</sup> analysis of 888 cases of biliary-tract disease, exclu-

<sup>1</sup> Scrimger, F. A. C.: Influence of Chronic Disease of Gall Bladder in Producing Stomach Symptoms, *Canadian Med. Assn. Jour.*, 1923, **13**, 235.

<sup>2</sup> Millet, G. W.: Cholecystectomy: Clinical and Pathological Findings in 200 Cases, *Northwest Med.*, 1925, **24**, 383.

<sup>3</sup> Blalock, W.: A Clinical Study of Biliary-tract Disease, *Jour. Am. Med. Assn.*, 1924, **83**, 2057.

sive of neoplasms, at the Johns Hopkins Hospital, he found the following percentage occurrence of symptoms:

	Per cent.
Pain . . . . .	96
Radiation of pain . . . . .	51
Indigestion . . . . .	86
Nausea . . . . .	76
Vomiting . . . . .	73
Constipation . . . . .	62
Eructation of gas . . . . .	59
Chills and fever . . . . .	62
Loss of weight . . . . .	66
Jaundice . . . . .	55
Itching of skin . . . . .	13

It is interesting also that in this same analysis he found that the liver was found enlarged on physical examination in 22 per cent of the cases, and that the gall bladder was thought to be palpable also in 22 per cent of the cases. The high incidence of jaundice in Blalock's cases is probably to be explained by the fact that cases of stone in the common duct are included in his study.

**Diagnosis of Chronic Cholecystitis.**—Because of the variety of symptoms which may be produced by a chronic inflammation of the gall bladder the diagnosis of the condition is often extremely difficult. It is easy in the advanced case which gives a history of recurrent attacks of pain in the right upper quadrant associated with nausea and vomiting, and still easier if there have been attacks of jaundice with these recurrent attacks of pain. But the diagnosis of the less obvious and of the less advanced cases present such difficulties that a host of other methods than the clinical history and examination have been devised to aid in their recognition. It is of course most desirable that cholecystitis should be diagnosed in its early and mild forms before it has had time to produce the serious effects which give rise to the classical clinical picture of the condition. The advantages of cholecystography and of the more well-known tests of hepatic function in this connection are discussed in other sections. It is particularly desirable also to be able to recognize functional disturbances. It seems fairly clear at the present time that the gall bladder can produce symptoms even when it does not present definite evidences of inflammatory disease. It has been a frequent experience of clinicians that the removal of a gall bladder which has shown a disappointingly small amount of evidence of inflammation has nevertheless often resulted in the prompt disappearance of symptoms of abdominal distress. This is particularly the case with many of the so-called "strawberry" gall bladders. We are accustomed to think in terms of functional disorders with reference to many other

organs, as for example, the heart, the kidneys, the endocrine glands, etc. But the idea is apparently so new as regards the gall bladder that it comes with unwelcome surprise, especially since so little is known at the present time about the normal functions of this organ. We feel, however, that cholecystography will be of distinct aid in the recognition of at least some of these functional disturbances. The reasons for this opinion are fully considered in the section dealing with cholecystography.

Palpation of the abdomen in many cases of chronic cholecystitis will give but little information of value. In most cases, however a manœuvre first described by J. B. Murphy will be found helpful. This consists in a sudden jab of the fingers upward under the right costal margin just as the patient has completed a deep inspiration. It is surprising how often this procedure will elicit tenderness which may otherwise be missed, in cases of subacute or chronic cholecystitis. In some cases a definitely enlarged liver may be made out. If a condition of hydrops of the gall bladder is present the enlarged organ can often be felt. Sometimes a gall bladder is enlarged to enormous size. Indeed the first operation performed on this organ was carried out by Johns S. Bobbs, of Indianapolis, in 1867 on the erroneous idea that he was going to operate upon an ovarian tumor. In patients with thin abdominal walls, not only can the gall bladder sometimes be felt but stones within it have actually been palpated through the abdominal wall. An enlarged palpable gall bladder must always be differentiated from a palpable kidney. Tenderness on pressure upon the lower dorsal vertebræ can sometimes be elicited, a sign which is felt by some to be of great value.

The importance of jaundice in a suspected case of cholecystitis is great when it is present but of no value when absent. Jaundice is much more likely to be present in the cases associated with stones, and in such cases it usually signifies a stone in the hepatic or common ducts. Stone in the cystic duct by itself cannot produce jaundice because it does not cause damming back of bile in the liver. When jaundice occurs with cystic-duct obstruction it is due to inflammatory extension into the liver with obstruction of the finer intra-hepatic bile channels. In obstructive jaundice the bile is carried from the liver chiefly by the lymphatics and enters the thoracic duct from which it is distributed throughout the body, as has been shown by the work of Bloom.<sup>1</sup>

Needless to say the old method of searching the feces for gall

<sup>1</sup> Bloom, W.: The Rôle of the Lymphatics in the Absorption of Bile Pigment from the Liver in Early Obstructive Jaundice, *Bull. Johns Hopkins Hosp.*, 1923, **34**, 316.

stones has become obsolete. In this connection, however, a source of confusion deserves mention. After the ingestion of a large amount of fat, soaps are sometimes formed in the alkaline intestine and these balls of soap are often mistaken by the patient for gall stones. The drinking of large amounts of olive oil is especially likely to cause the passage of these pseudo-gall stones which sometimes have facets and closely resemble true gall stones in appearance. This is the basis of many quack medicinal remedies for the removal of gall stones. The pseudo-stones melt readily on heating; and in this way they can be easily distinguished from the true ones. Occasionally, however, true gall stones that are passed by bowel are so large that they cannot escape detection. Indeed numerous cases are on record in which intestinal obstruction has been produced by a single large stone. We have operated upon a case in which a single stone, larger than a hen's egg, had ulcerated through the gall bladder into the jejunum and had completely obstructed its lumen.

In a case in which a previous operation for removal of calculi and drainage of the gall bladder has been performed and in which there is a return of symptoms of biliary colic, the presumptive evidence is strong that the recurrence of symptoms is due to gall stones.

It is important to bear in mind that in almost all cases of cholecystitis it is the inflammation and not the stones which is doing the damage to the patient. Diagnostic efforts should therefore be directed to the detection of disease of the gall bladder. The detection of stones is of secondary importance, although of course in a doubtful case the finding of gall stones by any method of examination, roentgen-ray or otherwise, is reassuring and enables one more certainly to incriminate the gall bladder as the cause of the patient's symptoms.

*Lyon's Method of Diagnosis.*—A special method devised by B. B. Vincent Lyon<sup>1</sup> for the diagnosis of cholecystitis, both acute and chronic, is based on the hypothesis of Meltzer of the contrary innervation of the gall bladder and sphincter of Oddi. Meltzer found that local douching of the duodenum with magnesium sulphate resulted in a relaxation of the duodenal wall and probably with it of the sphincter of the common bile-duct. To Lyon it seemed probable, on the assumption of the correctness of Meltzer's hypothesis of contrary innervation, that a relaxation of the duodenal wall and of the sphincter would be accompanied by a contraction of the gall bladder which would result in the emptying of its contents into the

<sup>1</sup> Lyon, B. B. V.: *Non-surgical Drainage of the Gall Tract*, 1923, Philadelphia, Lea & Febiger.



duodenum. Accordingly he devised a plan of instilling magnesium sulphate into the duodenum by means of a duodenal tube and of withdrawing samples of bile through the tube for examination. He uses from 50 to 100 cc. of a 33 (volumetric) per cent solution of magnesium sulphate which is equivalent to a 16.6 per cent of the magnesium salt itself, where the solution is made up in distilled water at 25° C. The first bile collected is usually diluted with a few cubic centimeters of the magnesium sulphate solution, but its color gradually deepens until it becomes apparently a pure bile of a light golden-yellow color and of medium viscosity, like that of syrup, and with healthy bile-ducts, perfectly transparent, except when a spurt of acid gastric juice enters the duodenum and mixes with the bile being collected, when an instantaneous emulsive turbidity is produced. After a few cubic centimeters of this bile have been withdrawn (which varies, perhaps, from 10 to 30 cc.) the bile suddenly deepens to a considerably darker golden-yellow and becomes noticeably more viscid, and usually transparent in healthy states, draining sometimes steadily, sometimes with slight intermittency until amounts have been recovered, which have varied from 10 to 300 or more cubic centimeters in pathological cases (10 to 75 cc. in normal cases), when a sudden transition in color and viscosity of the bile again appears, this time to a light transparent lemon-yellow and distinctly thinner and more limpid bile than either of the former types. This latter type of bile continues to flow with considerably greater intermittency as long as the relaxation of the common-duct sphincter is maintained. These three types of bile are designated "A," "B," and "C," respectively. The A bile is that obtained from the duodenum mixed with duodenal contents. The B bile is supposedly from the gall bladder and the C bile is hepatic bile. (See Plates IV and V.)

Lyon claims that by the gross and microscopic examination of the removed samples of bile it is possible to arrive at a very high degree of diagnostic efficiency in diseases of the bile tracts. It is impossible here to enter into the details of the findings and their significance in relation to different pathological states. For these Lyon's book should be consulted. The method has many enthusiastic adherents, but there are also many who consider it to have little real value. The evidence on both sides of the question has been presented by C. M. Jones.<sup>1</sup> Recently Martin<sup>2</sup> has shown that B bile can be con-

<sup>1</sup> Jones, C. M.: *The Rational Use of Duodenal Drainage: An Attempt to Establish a Conservative Estimate of the Value of this Procedure in the Diagnosis of Biliary Tract Pathology*, Arch. Int. Med., 1924, **34**, 60.

<sup>2</sup> Martin, Lay: *Biliary, Pancreatic and Duodenal Studies*, Arch. Int. Med., 1927, **39**, 343.

# PLATE IV

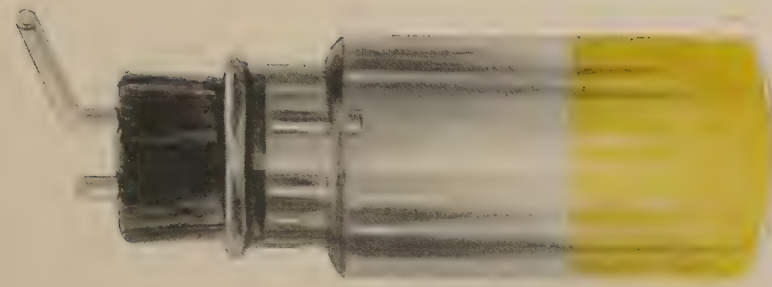
FIG. 1



FIG. 2



FIG. 3



Normal A, B and C Fractions of Bile. (Lyon.)

Fig. 1. Common duct bile (chiefly).

Fig. 2. Gall-bladder bile (chiefly).

Fig. 3. Liver bile (chiefly).



FIG. 1

FIG. 2

FIG. 3



Pathological B, Gall-bladder Fractions. (Lyon.)

Fig. 1. From case of splenomegaly with hemolytic jaundice with streptococcal infection. Fig. 2. Chronic cholecystitis with "masked" infection. Fig. 3. Chronic cholecystitis with "masked" infection and





verted into C bile and *vice versa* merely by altering the hydrogen-ion concentration. It is not certain that Meltzer's hypothesis is true, and it is improbable that the gall bladder can be emptied by Lyon's method, as is shown in the section on physiology. However, the procedure may be of considerable value in permitting the study of some of the gall-bladder contents, although it is by no means certain that cholecystitis will always reveal itself by a study of the contents of the gall bladder, since often the chief pathological findings are deep in the wall. Lyon also discusses in his book a method of recognizing pericholecystic adhesions by means of a tuning-fork.

**Differential Diagnosis.**—The conditions which are likely to be mistaken for chronic cholecystitis are numerous. The vague complaints of a patient with general visceroptosis are often ascribed to a chronic cholecystitis. It is in this type of case that great care is needed in arriving at a diagnosis. While it is true that stasis within the gall bladder, such as may be present in any case of severe visceroptosis, may be important in the production of inflammation and of the formation of biliary calculi, yet it frequently happens that opérations upon the gall bladder in this type of case yield very disappointing results. The importance of stasis as a factor in cholecystic disease has been particularly emphasized by Aschoff and more recently by Lütken. (See also Chapter VII.)

**Spastic Constipation.**—Chronic lesions of the colon, especially spastic constipation, or the so-called *mucous colitis*, are very often erroneously considered to be cases of cholecystitis. The clinical picture may be very confusing unless great care is exercised in eliciting a history and unless other aids are utilized in the examination. Cholecystography has been found of great assistance in making a diagnosis in this type of case. The patient with a spastic constipation will often complain of severe cramping pain in the right upper quadrant, even with nausea and vomiting; and on physical examination tenderness may be elicited in this region.

**Intestinal Allergy.**—A condition somewhat resembling this which is probably rather frequently confused with cholecystitis is that of intestinal allergy or anaphylaxis. The possibility of confusion caused by this condition has received almost no mention, but the importance of eliminating it in a diagnosis is very great. The symptoms can imitate very accurately those of recurrent attacks of cholecystitis. In a person who is subject to hayfever or asthma, unusual care should be taken to exclude intestinal allergy before arriving at a diagnosis of cholecystitis. Two cases have recently brought the matter to our attention in a forcible manner. In one

case, the patient had been operated upon elsewhere for supposed chronic cholecystitis. The surgeon was surprised to find a gall bladder of normal appearance, but he nevertheless established drainage. While in the hospital the patient was relatively free from symptoms, but later the old symptoms recurred. He was found to be a sufferer from hayfever and asthma and to be sensitive to wheat, the ingestion of which produced his supposed gall-bladder symptoms. When he abstained from wheat he was free from his symptoms. The second patient under the care of Drs. Eyerman and Clopton, also was one who was sensitive to wheat. She had rather typical symptoms of chronic cholecystitis and presented herself for an operation upon her gall bladder. A cholecystographic examination, however, showed a normal gall bladder, and later Dr. Eyerman found that she was suffering from intestinal allergy. By abstaining from wheat she has had no attacks of supposed cholecystitis. This question is discussed separately in an article by Alexander and Eyerman.<sup>1</sup>

*Carcinoma of the Hepatic Flexure.*—Carcinoma of the hepatic flexure is sometimes mistaken for chronic cholecystitis, but a roentgen-ray examination of the alimentary tract should reveal such a lesion in a satisfactory manner.

*Chronic Appendicitis.*—Chronic appendicitis may also give rise to symptoms closely resembling those of chronic cholecystitis. The two conditions frequently are associated, and both may be corrected through the same incision. The most serious aspect of the confusion is that frequently the appendix is removed and nothing is done to the gall bladder which may be the more serious offender.

*Diseases of the Liver.*—Various diseases of the liver often present problems in diagnosis in which there is great difficulty in deciding whether or not the chief cause of the trouble is a cholecystitis. The cases of enlarged, slightly tender liver with slight jaundice are particularly troublesome. The various types of cirrhosis of the liver are conditions which are particularly likely to be confused with chronic cholecystitis. The presence of ascites and other signs of portal obstruction are of course very important in making a differentiation. Cholecystography is often of no assistance in these cases because the gall bladder is frequently not visualized even when there is no inflammation present. The failure of visualization in these cases probably lies in impaired excretion of the dye through the liver and in failure of its concentration because of edema of the gall bladder. It should not be forgotten, however, that biliary cirrhosis is asso-

<sup>1</sup> Alexander, H. L. and Eyerman, C. H.: Food Allergy in Henoch's Purpura, *Am. J. of Diseases of Children*, 1927, **16**, 322.

ciated with and probably due to a long-standing infection of the gall bladder and biliary ducts. An exploratory laparotomy is often necessary to clear up the diagnosis. Syphilis of the liver is one of those conditions which, because of pain, jaundice and fever, is often confused with cholecystitis. A strongly positive Wassermann reaction in the presence of these symptoms should arouse suspicion as to the presence of a syphilitic hepatitis.

*Lesions of the Spine.*—Another important group of conditions to differentiate from cholecystic disease comprises the lesions of the spine. In Pott's disease of the lower dorsal vertebræ the pain is frequently referred around to the upper right quadrant of the abdomen, and there may even be spasticity of the abdominal muscles on the right side. It has been a common experience to mistake vertebral lesions for gall-bladder disease. Roentgen-ray examination of the spine will serve to rule out the possibility of such conditions in doubtful cases.

*Intrathoracic Inflammatory Lesions.*—Intrathoracic inflammatory lesions on the right side provide another source of confusion in diagnosis. These are more likely to come up for consideration in cases of suspected acute cholecystitis; but nevertheless chronic pleurisies, either pyogenic or tuberculous, may give symptoms suggestive of cholecystitis. An examination of the chest should serve to rule out these conditions.

*Lesions of the Stomach and Duodenum.*—Chronic lesions of the stomach and duodenum are also likely to be confused with chronic cholecystitis, especially chronic peptic ulcer. Not infrequently the gall bladder is adherent to a duodenal ulcer; again even when it is not adherent there is often a simultaneous chronic cholecystitis with or without stones, coëxisting with a peptic ulcer. Other lesions of the stomach also, such as carcinoma, syphilis, etc. may present symptoms suggestive of chronic cholecystitis. For these reasons it is our own custom, in the majority of cases of suspected chronic cholecystitis, to examine the alimentary tract with the barium meal and the roentgen-ray. Conversely, it is our custom also to examine most cases of suspected peptic ulcer by means of cholecystography. Recently we have seen 2 cases in which the patients had pseudo-diverticula of the duodenum which were thought at first to be responsible for the symptoms of abdominal distress, but in both cases the trouble was in reality due to chronic cholecystitis as shown by the fact that cholecystectomy resulted in complete relief. A discussion of this question together with that



of the possible confusion between chronic cholecystitis and chronic duodenal ileus is given in the article by Larimore and Graham.<sup>1</sup>

*Lesions of the Kidney.*—Chronic lesions of the kidney, such as pyelitis or pyonephrosis, kidney stone and hydronephrosis may all give symptoms suggestive of chronic cholecystitis. However, they can practically always be excluded by a careful history and a careful examination which should include if necessary not only an examination of the urine but roentgen-ray studies by pyelography as well.

*Hemolytic Icterus.*—Hemolytic icterus, due to various causes, is often mistaken for cholecystitis. In the cases of familial icterus the situation is sometimes complicated by the fact that gall stones are present. However, the enlarged spleen, the increased fragility of the red blood cells, the van den Bergh test and the history will usually serve to make the diagnosis of hemolytic icterus.

*Slipping Rib.*—An interesting but rare condition which sometimes is confused with chronic cholecystitis is that of "slipping rib" in which the eleventh rib on the right side overrides the rib above it and thus causes attacks of pain. The diagnosis is made by feeling the rib slip up when the patient assumes the right position for it to do so. Removal of the rib has resulted in complete relief of the symptoms in the few cases observed. We have had no personal experience with the condition.

*Specific Infections.*—Chronic cholecystitis due to specific chronic infections, such as tuberculosis, syphilis, actinomycosis has been described but in no instance has the diagnosis been made during life. The symptoms presumably would be about the same as those due to non-specific chronic cholecystitis. It is a strange thing that syphilis of the gall bladder seems to be almost unknown. Just as syphilis of the stomach has come to be recognized only within about the last twenty years it is possible that syphilitic lesions of the gall bladder may become more frequent if attention is directed to their possibility. Rolleston<sup>2</sup> prophetically remarks, "it would be natural to expect that both tuberculosis and syphilis would play a more considerable part than is at present recognized in the production of chronic cholecystitis." One case of actinomycosis of the gall bladder was described by Robson<sup>3</sup> in 1905. A report of 2 cases

<sup>1</sup> Larimore, J. W. and Graham, E. A.: Diverticula and Duplication of the Duodenum, with Reference to the Importance of Cholecystitis in the Production of Symptoms, Surg., Gynec. and Obst., 1927, 45, 257.

<sup>2</sup> Rolleston, H.: Diseases of the Gall Bladder and Bile-ducts, Oxford Med., 1925, vol. III, part I, p. 443.

<sup>3</sup> Robson, A. W. M.: Actinomycosis of the Gall Bladder, Med. Chir. Trans., London, 1905, 88, 225

of tuberculosis of the gall bladder together with a discussion of their varieties is given by Simmonds.<sup>1</sup>

### PARASITIC DISEASES OF THE GALL BLADDER.

*Echinococcus* infections are rare in the gall bladder, although common in the liver. Cysts are not infrequently found in the lumen of the gall bladder which have come down from the liver; but a true echinococcus cholecystitis implies of course an actual infection of the wall. Of these comparatively few have been reported. Rolleston states that he has references to seven reported cases.

Invasion of the gall bladder by *ascaris lumbricoides* (roundworm) is less common than the invasion of the bile-ducts alone. Aviles<sup>2</sup> has reported a case and has reviewed the literature.

Cases of *distomiasis* have occurred in which the liver flukes have been found in the gall bladder.

Only exceptionally have any cases of the parasitic diseases of the gall bladder been diagnosed during life. The symptoms produced are practically the same as those seen in acute or chronic cholecystitis from any other cause.

### DIAGNOSIS OF CHOLECYSTITIS AT OPERATION.

Of equal importance with the clinical diagnosis of cholecystitis is the establishment of a pathological diagnosis at operation. What are the criteria upon which the surgeon at laparotomy shall make his decision as to whether or not a particular gall bladder is diseased? With the present tendency to operate upon cases of cholecystitis at a much earlier stage than formerly, this question has become of increasing importance. Formerly it was the custom to recommend operation only after the pathological effects had reached an advanced stage; these late effects were correspondingly easy to recognize at operation. But at the present time the surgeon is often at a loss to tell whether a gall bladder is really diseased or not, even when at the opened abdomen he has an opportunity to see it and to feel it.

Certain characteristics of course speak very definitely in favor of disease, or at least of abnormality. These are thickening, change of color from the normal slate-blue to gray or pink, adhesions and stones. When these changes are present there can be no doubt as to the fact

<sup>1</sup> Simmonds: Ueber Gallenblasentuberkulose, Verhandl. d. Deutsch. path. Gesell., 1910, p. 332.

<sup>2</sup> Aviles, J.: The Rôle of Ascariasis in Gall-bladder Disease, Surg., Gynec. and Obst., 1918, 27, 459.

that the gall bladder is at least not normal. The cases with less advanced pathological changes reveal less conspicuous evidence of disease or abnormality, but nevertheless many of them can be detected. We feel that the presence of an enlarged gland at the junction of the cystic and common ducts (Lund's sentinel gland) is fairly good evidence of some degree of inflammation in the gall bladder. We feel also that definite evidence of hepatitis, either recent or old, is strongly suggestive of cholecystitis. This idea is in line with our hypothesis concerning the pathogenesis of cholecystitis which is discussed in Chapter III. In cases of acute cholecystitis the liver is often enlarged with rounded edge. In the more chronic cases one often sees more or less hepatic fibrosis. This may vary from scarring beneath the capsule to a definite biliary cirrhosis. A rather common finding which we regard as especially significant in cases of relatively mild chronic cholecystitis is a subcapsular fibrosis of the liver which reveals itself in a reticulated mass or in striations of white scar tissue involving the upper and sometimes the under surface of the right lobe and extending upward from the region of the gall bladder. (Fig. 80.) Special attention has been directed to this scarring also by Weible<sup>1</sup> who states that he found it in 64 per cent of 55 cases of chronic cholecystitis. Some surgeons prefer to open the gall bladder to inspect its mucosa when in doubt as to the presence of disease. We have not found this procedure to be particularly helpful, although at times a strawberry gall bladder can be recognized in this way. It does happen rather frequently, however, that a gall bladder distended with bile may seem normal, but after removing some of the bile by means of either an incision, or better by a syringe, stones may be felt which otherwise would have been missed. A distended gall bladder can never be palpated satisfactorily. We do not feel that squeezing the gall bladder with the fingers to determine whether or not it can be emptied is of any value in diagnosis, and we feel that it may occasionally be harmful in perhaps forcing small undetected stones or infected bile out of the gall bladder into the ducts. We consider it as a custom which should be condemned. If there is an obstruction of the cystic duct with hydrops this condition can be recognized from the general appearance of the organ in addition to the appearance of its contents obtained by a syringe. Ritchie,<sup>2</sup> however, and others lay great stress on the importance of determining the col-

<sup>1</sup> Weible, R. E.: Visible Changes in the Liver in Chronic Cholecystitis, *Surg., Gynec. and Obst.*, 1925, **40**, 94.

<sup>2</sup> Ritchie, H. P.: The Surgical Diagnosis of Gall-bladder Disease, *Minnesota Med.*, 1923, **6**, 683.

lapsibility of the organ. Moynihan<sup>1</sup> has called attention to the fat on the gall bladder as an important sign of chronic inflammation.

It is particularly important to examine the neck of the gall bladder, and to do this properly it is necessary to have exposure sufficient to permit adequate inspection. One often finds adhesions joining the under surface of the gall bladder in this region to the duodenum or other structures. These are of course distinct from the hepato-duodenal ligament which encloses the cystic duct. We have repeatedly found this evidence of disease in a gall bladder which otherwise appeared normal, and we have found that cholecystectomy

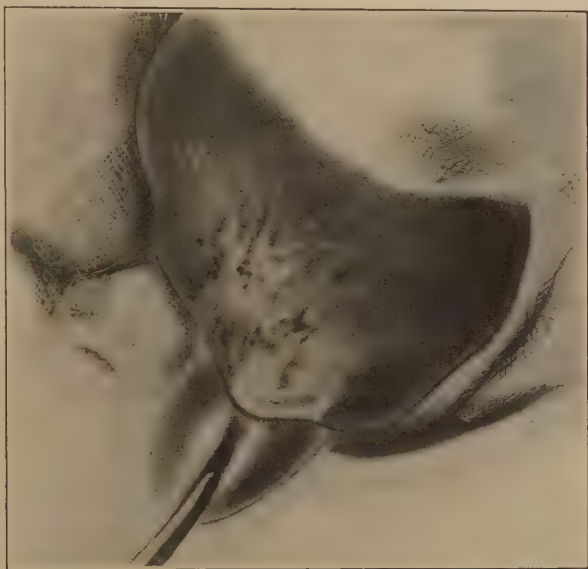


FIG. 80.—Subcapsular fibrosis and scarring of right lobe of liver which is commonly seen in association with chronic cholecystitis. See text for discussion.

in such cases usually is followed by complete relief of symptoms. In order to obtain proper exposure for inspection of this field it is necessary to lift the fundus anteriorly and upward.

Except for the fact that many surgeons regard thick, tar-like bile as an evidence of disease of the gall bladder, it would seem unnecessary to state that, since concentration of the bile is one of the well-known functions of the gall bladder, the finding of thick tar-like bile is merely an evidence that the organ is carrying on its normal

<sup>1</sup> Moynihan, B.: The Early Signs and Symptoms of Cholelithiasis, *British Jour. Surg.*, 1922, **10**, 127.



function of concentration. Such a finding, therefore, should not be regarded as a sign of disease.

The common duct should always be examined by palpation of as much of it as possible. This is accomplished best by inserting the index finger into the foramen of Winslow and feeling the duct between that finger and the thumb. Our customary manœuvre is, when standing at the patient's right, to insert the index finger of the left hand into the foramen. This sort of palpation permits the examination not only of a considerable portion of the common duct but of the head of the pancreas as well. When the result is negative it is of little value, but sometimes an unsuspected stone in the duct can be found in this way, and nearly always an enlargement of the head of the pancreas can be readily detected. The detection of a stone in the region of the ampulla may be very difficult. Procedures which are used for this purpose when necessary are probing of the common duct, mobilization of the duodenum to permit more adequate palpation of this region and sometimes even an incision into the duodenum to permit inspection of the biliary papilla.

### TUMORS OF THE GALL BLADDER.

**Benign Tumors.**—Benign tumors of the gall bladder are comparatively rare, unless one regards the hyperplasia of the villi such as occurs in many cases of chronic cholecystitis as a true papilloma. MacCarty<sup>1</sup> has made a special study of this condition. He finds that the villi in the "strawberry" gall bladders are often much enlarged. Sometimes they are branched and so large that they form true papillomas, which may be single or multiple. Microscopically these papillomas present the same appearance as the villi of the "strawberry" gall bladder. They are merely larger and more branched. He states also that in 5000 gall bladders removed at the Mayo Clinic 4 per cent showed distinct papillomas. In the experience of most others, however, papilloma is much less common. There are no special symptoms which distinguish it clinically from an ordinary chronic cholecystitis. Carman, however, recognized a case by cholecystographic examination. In 7 of the 8 cases collected by Sand and Mayer<sup>2</sup> the papilloma was associated with gall stones. Other benign tumors that have been described are fibroma, cystic adenoma and cysts of various kinds other than

<sup>1</sup> MacCarty W. C.: "Strawberry" Gall Bladders, *Ann. Surg.*, 1919, **69**, 131.

<sup>2</sup> Sand, R. and Mayer, L.: Transformation de la Vésicule Biliaire Tout Entière en un Kyste Papillifère, *Arch. de med. exper. et d'anat. path.*, 1911, **23**, 523.

hydatids. Walthard<sup>1</sup> has recently reported a case of diffuse fibromatosis of the gall bladder.

**Carcinoma.**—Primary carcinoma of the gall bladder is of much more common occurrence than is generally supposed. It constitutes approximately 5 or 6 per cent of all cases of carcinoma. It has a very definite relationship to biliary calculi. In reported series of cases gall stones have been found in from 69 (Musser<sup>2</sup>) to 100 per cent (Janowski<sup>3</sup>). The relationship to calculi is shown, however, in a more striking manner by the fact that, according to Rolleston,<sup>4</sup> from 4 to 14 per cent of all cases of cholelithiasis are associated with carcinoma of the gall bladder. In our own cases at the Barnes Hospital 8.5 per cent of all cases of stones in the gall bladder have been associated with carcinoma. Also, that the calculi have apparently a part in the production of the carcinoma, instead of being formed as a result of it, is shown by the analysis of Rolleston, who quotes Siegert as having found calculi in 94 of 99 cases of primary carcinoma, but only twice in 13 cases in which there were metastatic growths in the gall bladder. Rolleston states that in 13 other cases of his own series of metastatic involvement of the gall bladder calculi were present in only 1. In these 26 cases, therefore, of secondary growth in the gall bladder, gall stones occurred in 3, or 11.7 per cent, which are within the limits, 5 to 12 per cent, of the incidence of gall stones in ordinary routine postmortem work. Lentze<sup>5</sup> has recently studied the question and collected a long bibliography on the subject. He found that in 557 cases of cholelithiasis there was a cancer of the gall bladder in 5.1 per cent of women over thirty-nine years of age. The percentage was 4.3 in both sexes. He considers cholelithiasis the primary condition. Finsterer<sup>6</sup> has found the association of cancer and stones so frequently that he regards familial occurrence of cancer as one of the indications for surgical intervention in cholelithiasis. In this country, Deaver and Bortz<sup>7</sup> found that out of 903 cases of gall-bladder disease, 1.5 per cent

<sup>1</sup> Walthard, B.: Diffuse Fibromatosis of Gall Bladder, *Zentralbl. f. Chir.*, 1925, 52, 341.

<sup>2</sup> Musser: Primary Cancer of the Gall Bladder and Bile-ducts, *Boston Med. and Surg. Jour.*, 1889, 121, 525.

<sup>3</sup> Janowski, W.: Ueber Veränderungen in der Gallenblase bei Vorhandensein von Gallensteinen, *Ziegler's Beitr. z. path. Anat.*, 1891, 10, 449.

<sup>4</sup> Rolleston, H.: Diseases of the Liver, Gall Bladder and Bile-ducts, 1905, Philadelphia, W. B. Saunders Company, p. 629.

<sup>5</sup> Lentze, F. A.: Gallensteine und Gallenblasencarcinom, *Beitr. z. klin. Chir.*, 1926, 137, 38.

<sup>6</sup> Finsterer: Erfolge und Misserfolge bei Gallensteinoperationen, *Med. Klin.*, 1926, 22, 1914.

<sup>7</sup> Deaver, John B. and Bortz, E. L.: Gall-badder Disease: A Review of 903 Cases, *Jour. Am. Med. Assn.*, 1927, 88, 619.

showed carcinoma of the gall bladder. The latter figures more nearly agree with those of Lotzin.<sup>1</sup> He found, in 2943 autopsies performed in the period from 1919 to 1925, undoubted primary carcinoma of the biliary passages in 27 instances (about 1 per cent). Carcinoma without stone formation was found more frequently in males than in females. Lotzin believes that carcinoma of the gall bladder and ducts and stone formation are independent of each other.

It is a matter of the greatest importance from the standpoint of cancer prevention to emphasize this scarcely realized fact that 1 person in about 25 who have gall stones will have a carcinoma of the gall bladder. The mortality-rate of operations for gall stones seems to be less than the risk of cancer. How the calculi act to produce a carcinoma can of course not be answered satisfactorily with our present ignorance as to the origin of malignant tumors, but the temptation is strong to assume that the factor of chronic irritation of the mucosa induced by the stones must be important. Ewing thinks that in addition to the mechanical effect of the calculi, the presence of cholesterol and the irritative and digestive action of the bile are important factors. Leitch,<sup>2</sup> in a very interesting article, reports the experimental production of carcinomatous growth in the gall bladders of guinea-pigs by the implantation of gall stones and pebbles into the lumen of the organ.

Because of the close relationship which exists between calculi and carcinoma, it is not surprising to find that carcinoma of the gall bladder occurs four or five times as frequently in women as in men. This incidence is in striking contrast to that of primary carcinoma of the bile-ducts which is slightly more common in males. It is significant that gall stones are less frequently associated with carcinoma of the bile-ducts than with carcinoma of the gall bladder. As might be expected cancer of the gall bladder is a disease of middle and old age. The average age in both Futterer's and Winton's series (quoted by Rolleston) was fifty-eight years.

In appearance a primary carcinoma of the gall bladder belongs usually to one of three types: (1) Papillary; (2) gelatinous; (3) infiltrating. The papillary tumors grow into the lumen as a coarse irregular mass which ultimately distends and completely fills the organ. They probably arise from papillomatous outgrowths of the

<sup>1</sup> Lotzin, R.: The Relation of Gall Stones to Carcinoma of the Extrahepatic Biliary Passages and a Contribution on the Migration of Gall Stones and Hydrops of Biliary Passages, *Arch. f. klin. Chir.*, 1926, **139**, 525.

<sup>2</sup> Leitch, A.: Gall Stones and Carcinoma of the Gall Bladder: An Experimental Study, *British Med. Jour.*, 1924, ii, 451.

mucosa similar to the papillomas described above in connection with the benign tumors. Microscopically these carcinomas are adenomatous in type; and the elongated vascular papillæ are lined with cylindrical epithelium. Extensive secretion of mucus may occur but is less conspicuous than in the gelatinous type. These tumors tend to spread through the wall and to involve the peritoneum, but metastases to the liver do not occur early. Extensive adhesions to adjacent viscera may be present. The gelatinous carcinomas form large bulky tumors with early metastases to the liver, the peritoneum and the lymph glands. In this type the over-secretion of mucus is a conspicuous feature. These tumors also are adenocarcinomas microscopically. Ewing<sup>1</sup> states that next to the stomach the gall bladder is the most frequent source of gelatinous carcinoma of the peritoneum. The infiltrating type of carcinoma begins usually as a localized lesion of a chronically inflamed mucosa. The wall is involved early and becomes diffusely thickened. Metastases occur early. These tumors appear, when well developed, as hard masses, about the size of or smaller than a normal gall bladder, densely adherent to surrounding structures and with extensive nodular metastases in the liver. Microscopically these tumors show much fibrous tissue surrounding adenomatous groups of cells, but in the metastases the fibrosis is much less conspicuous. It is probable that much of the extensive fibrosis seen in the gall bladder is the result of long-standing inflammatory change preëxistent to the carcinoma. Squamous-celled carcinomas, according to Rolleston, occur rather frequently, in which typical epithelial pearls and prickle cells may be seen. Metastases of all of the varieties of these carcinomas may occur in any part of the body, but they are much more frequent in the abdominal organs than elsewhere. Of the abdominal organs the liver is by far the most frequently involved. Ascites is not an uncommon complication; and peritonitis may occur following a perforation of the tumor. Fistulous tracts into other hollow organs and even externally are fairly common developments in the late stages. (Figs. 81 and 82.)

The clinical picture is not characteristic. The symptoms are chiefly of two kinds: (1) Those due to the chronic cholecystitis; (2) those due to the tumor, either local or metastatic. A hard mass may sometimes be felt through the abdominal wall but of course the same sort of finding may be obtained on palpation in a case of non-malignant cholecystitis. Most cases of carcinoma give a

<sup>1</sup> Ewing, J.: *Neoplastic Diseases*, 1922, Philadelphia, W. B. Saunders Company, p. 695.



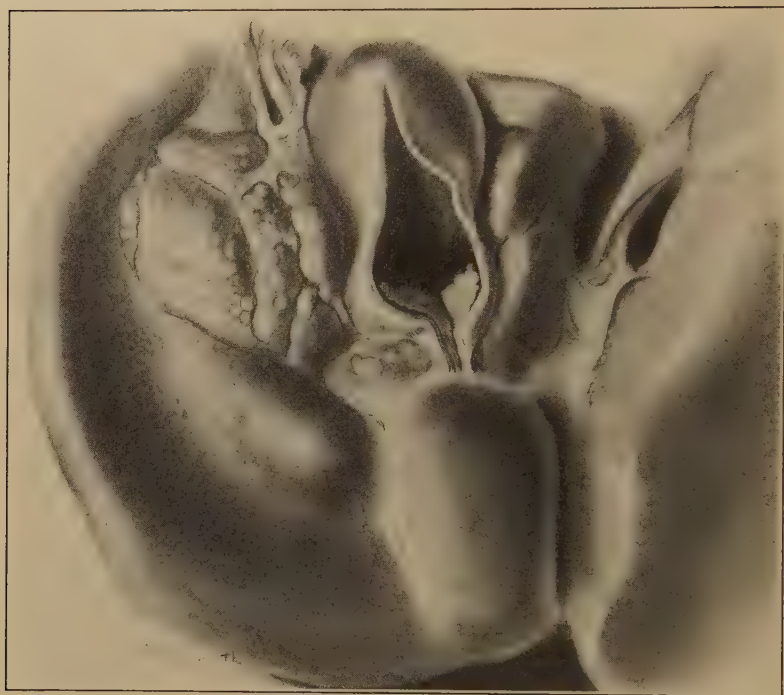


FIG. 81.—Carcinoma of cystic duct with extensive metastases into liver.

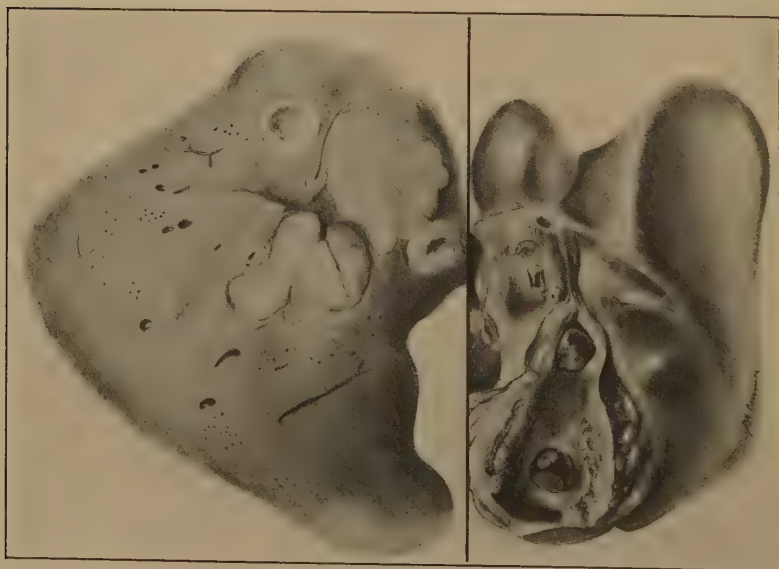


FIG. 82.—Carcinoma of gall bladder with metastases in liver associated with cholelithiasis.

history suggestive of chronic cholecystitis and cholelithiasis extending back for many years. One of the most characteristic clinical features is the occurrence of persistent and progressive jaundice in a patient who presents a history of long-standing cholecystitis. Such jaundice is usually due to metastatic involvement of the liver. Jaundice due to inflammations of or to stones in the ducts is almost always intermittent in character. In atrophic cirrhosis, however, there may be a progressive jaundice together with symptoms somewhat suggestive of a chronic cholecystitis; in both conditions also ascites is likely to be present. The recognition of fistulous tracts into other organs or through the skin, and suspicious evidence of metastases all speak strongly for a malignant growth in the gall bladder. Roentgen-ray and other laboratory procedures are of little help in making a specific diagnosis, but they may, by giving evidence of a cholecystitis, direct attention to the gall bladder as the site of a suspected carcinoma. The demonstration, by means of a barium meal, of a fistulous tract between the intestine and the gall bladder will be strong but not conclusive evidence of a carcinoma. In the majority of cases the diagnosis can be made with certainty only by a laparotomy. It is important in suspected cases to perform a laparotomy, because sometimes one will be gratified to find that no carcinoma is present and that the jaundice is due only to an impacted stone in the common duct. When carcinoma is present and sufficiently advanced to cause jaundice from metastases in the liver, the duration of life is usually not more than six months.

**Sarcoma of the Gall Bladder.**—Sarcoma of the gall bladder is a rare condition. We have had no personal experience with this type of tumor. Like carcinoma, it seems to have arisen on the basis of a chronic cholecystitis in all the cases so far reported. Also, calculi are frequent, as in carcinoma. Ewing states that it appears that two forms of sarcoma arise on the basis of a chronic cholecystitis, one derived from an overgrowth of smooth muscle cells, the other from the inflammatory new growth of connective tissue and blood-vessels. In the type of myosarcoma the wall of the gall bladder is much thickened. Carson and Smith<sup>1</sup> have reported an interesting case of the second type in which there was a localized nodular thickening of the wall, 8 cm. in diameter, composed almost entirely of round cells. It is necessary of course to add a word of caution about the microscopic diagnosis of sarcoma, since these tumors seem to occur only on the basis of a chronic inflammation which is notori-

<sup>1</sup> Carson, N. B. and Smith, George M.: Primary Sarcoma of the Gall Bladder, *Ann. Surg.*, 1915, **62**, 688.

ously varied in its cellular characteristics. There are no symptoms or other clinical features which serve to distinguish a sarcoma of the gall bladder.

### INJURIES OF THE BILIARY PASSAGES.

The biliary passages are subject to both direct and subcutaneous injuries. The direct injuries produced by penetrating wounds require no special discussion. Of greater interest are the subcutaneous injuries which, as in the case of other abdominal viscera, may follow blows of various kinds to the abdomen without piercing the abdominal wall. Courvoisier collected 34 examples of this kind, due to the following injuries:

	Cases.
Flat falls on the abdomen . . . . .	7
Falls on the abdomen against sharp edges or corners . . . . .	4
Run over . . . . .	6
Local blows from kicks, fists, etc. . . . .	13
Bruise by locomotive bumper . . . . .	1
Bruise by carriage wheel . . . . .	1
Strain . . . . .	1
Not stated . . . . .	1
The various injuries involved:	
Gall bladder . . . . .	14
Cystic duct . . . . .	1
Hepatic duct . . . . .	3
Choledochus . . . . .	4
Not stated . . . . .	12

The chief dangers of such wounds are of course peritonitis from the escape of bile into the abdominal cavity and hemorrhage. In 12 of Courvoisier's 34 cases the patients recovered. With modern surgery a much higher percentage of recovery should be expected.

### TORSION OF THE GALL BLADDER.

Torsion of the gall bladder is a rare condition of which Shipley<sup>1</sup> has recently collected 22 examples including 1 of his own. He states that it is necessary to distinguish between partial and complete torsion. In the former condition the clinical picture closely resembles that of chronic cholecystitis, but in the latter it is that of an acute intra-abdominal condition. It is possible for torsion to occur probably only in those cases in which the entire gall bladder is covered with peritoneum and hangs freely. In such cases it is attached to the liver by a short mesentery which extends along the cystic duct and usually ends near the point where the cystic duct

<sup>1</sup> Shipley, A. M.: Torsion of the Gall Bladder, *Arch. Surg.*, 1927, **14**, 968.

joins the gall bladder. It is the asthenic type of individual in whom torsion occurs, and in 20 of Shipley's 22 cases the patients were women, usually over sixty years of age. The gall bladder showed different degrees of necrosis in 20 cases. In the other 2 cases the torsion was somewhat less than 360 degrees. Of the 22 cases, 7 were clockwise, 5 were counter-clockwise, and in 10 cases the direction was not mentioned. In all except 2 of the cases the onset of symptoms was sudden, with pain in the right upper quadrant as the outstanding symptom. Vomiting was nearly constant; in 3 cases ileus was suspected. In most of the cases a moderate amount of bloody serous fluid was found in the peritoneal cavity. In some cases there were loose, thin recent adhesions, but usually the delivery and removal of the gall bladder was easy. The outstanding pathological feature was necrosis of the organ due to strangulation of its blood supply. Its walls were thickened and infiltrated with blood, and its cavity was also usually filled with blood. It was nearly always enlarged, distended, smooth, and was often described as kidney-shaped or sausage-shaped. In many of the cases the enlarged gall bladder could be felt through the abdominal wall. Jaundice was not present in any of the cases. Stones were reported in only 7 of the cases and never in any of the ducts. Fever was not a constant symptom. Symptoms of shock were not normally present. In only 1 case was the correct diagnosis made before operation. In most cases the preoperative diagnosis was acute cholecystitis, ileus, or acute appendicitis. In 21 of the cases cholecystectomy and drainage of the subhepatic space was carried out. Seventeen of the 21 recovered.



## CHAPTER VI.

### BILE-DUCTS.

#### CONGENITAL OBLITERATION OR ABSENCE OF BILE-DUCTS.

IN the chapter on Anatomy variations from the normal arrangement of the bile-ducts have been discussed and brief mention has been made of the condition often called congenital obliteration or absence of the bile-ducts.

In this condition several variations are found as regards the location and the extent of the defect. The hepatic duct may be absent or impervious, the hepatic and cystic ducts impervious, the gall bladder and cystic duct absent, the gall bladder rudimentary, the cystic duct obliterated, the common duct absent except for a fibrous cord, etc. In Milne's<sup>1</sup> cases the most frequent location of the obliteration was at the lower end of the common duct, but in the cases collected by Howard and Wolbach<sup>2</sup> the cystic and hepatic ducts were the most common sites. Males are slightly more commonly affected than females. In some instances more than one member of the same family has been affected. Feldman and Lawson,<sup>3</sup> however, have reported an interesting case in which the condition occurred in only one of a pair of twins. Although Holmes<sup>4</sup> in 1919 could find records in the literature of only slightly more than 100 cases, the condition is probably actually more frequent than these figures would signify. For example, in the St. Louis Children's Hospital, since 1919 we have had 3 cases, verified by either operation or postmortem examination, none of which have been reported.

**Pathology.**—In the most extreme cases, only fibrous cords exist where the extra-hepatic ducts normally are located. There are nearly all possible gradations between this extreme picture of the

<sup>1</sup> Milne, L. S.: Congenital Atresia of the Bile Passages, *Quart. Jour. of Med.*, 1911-1913, **5**, 409.

<sup>2</sup> Howard, C. P. and Wolbach, S. B.: Congenital Obliteration of the Bile-ducts, *Arch. Int. Med.*, 1911, **8**, 557.

<sup>3</sup> Feldman, W. M. and Lawson, M. A.: A Case of "Congenital" Occlusion of the Common Hepatic Duct in a Twin Baby, with an Indirect van den Bergh Reaction, *Lancet*, 1924, **ii**, 113.

<sup>4</sup> Holmes, J. B.: Congenital Obliteration of the Bile-ducts, *Johns Hopkins Hosp. Rep.*, 1919, **18**, 75.

condition and the normal. In less extreme cases, a part or in fact nearly all of the duct system is patent. In practically all cases, however, there is a definite thickening and fibrosis of the ducts even in their patent parts. Associated with the abnormalities of the ducts there is also found a cirrhosis of the liver in the great majority of the cases. The liver is nearly always enlarged and is intensely bile-stained, usually of a dark-green color. Its surface is irregular and resembles very much the surface of the liver in ordinary atrophic cirrhosis. It cuts with increased resistance, and it is plainly evident that an unusually large amount of fibrous tissue is present. Microscopically, the excessive fibrous tissue is seen in some places to surround individual lobules and in other places to surround groups of lobules, separating them from other groups. The process therefore represents both a monolobular and a multilobular cirrhosis. Pile pigment is present everywhere throughout the liver, and the small bile-ducts are often plugged with inspissated bile. Proliferation of the parenchymatous cells which sometimes occurs gives rise to the appearance of pseudo-bile canaliculi, as in ordinary cirrhosis. Ascites is frequently present, and the spleen is generally enlarged. In 2 of our 3 cases there was no evidence at all of any gall bladder. In the third case a very small pear-shaped structure which was found was filled with mucus. This was thought to be a rudimentary gall bladder. In only 1 of the 3 cases was a postmortem examination made, and in that one there was found a chronic interstitial inflammation at the hilus of the liver with scar formation and obliteration of the common duct. In the other 2 cases no evidence of bile-ducts was found at operation.

Hess,<sup>1</sup> in addition to describing a case, has discussed the question of the pancreatic ducts in cases of congenital obliteration of the bile-ducts. In his case which lived to the age of three months there was found at autopsy a complete obliteration of all the extra-hepatic bile-ducts and the papilla of Vater, and a marked hypoplasia of the gall bladder. There was an anomalous position of the accessory pancreatic duct (the duct of Santorini). He states that when the common duct is congenitally absent its loss is usually compensated for, as regards pancreatic secretion, by the duct of Santorini which permits pancreatic juice to enter the duodenum; but that in some cases the obliteration of the excretory apparatus of the pancreas is total and complete. In such cases the duct of Wirsung is obstructed, and the accessory duct of Santorini absent. He

<sup>1</sup> Hess, A. F.: The Pancreas and its Ducts in Congenital Obliteration of the Bile-ducts, *Arch. Int. Med.*, 1912, **10**, 37.

considers therefore that cases of congenital absence of the bile-ducts can be divided into those with compensated and those with uncompensated pancreatic obstruction.

**Pathogenesis.**—The origin of this condition has aroused much discussion. There is scant evidence in favor of a syphilitic origin. Partly based on the analogy that certain poisons, such as toluylen-diamin for example, after reaching the liver produce cirrhosis and cholangitis, Rolleston proposes the view that there is a primary cirrhosis of the liver, due to poisons conveyed by the umbilical vein during fetal life, which causes a descending and obliterative cholangitis of the extra-hepatic ducts which more readily become obstructed on account of their comparatively small lumen than in later life. On the contrary, John Thomson,<sup>1</sup> Milne,<sup>2</sup> Foote and Hamilton,<sup>3</sup> and others have believed that the cirrhosis of the liver is secondary to the biliary obstruction caused by a developmental aplasia or narrowing of the ducts. Frensdorf<sup>4</sup> is inclined to agree with Rolleston's view, as are also Merle and Petit.<sup>5</sup>

**Symptoms and Clinical Course.**—The child may be jaundiced at birth. If not he becomes jaundiced generally within the first few days, although in some cases the icterus has not been observed until several weeks after birth. During the early part of the course the jaundice is the most striking feature of the clinical picture. It is usually progressive, but in some cases it is said to have diminished at times, followed later by another increase. In the late stages the child develops a deep brown or an olive-green color. The stools are usually clay-colored from the start, although at times in certain cases they are said to have contained bile. Hess comments on this feature and attributes the occasional finding of bile to an excretion of it from the blood stream through the wall of the intestine. The urine is deeply bile-stained. Curiously enough, in 1 case Feldman and Lawson<sup>6</sup> found the van den Bergh test to be indirect. Hemorrhages are frequent, and are often the immediate cause of death. They may be subcutaneous and also from any of the orifices of the body. Bleeding from the umbilical cord may be severe.

<sup>1</sup> Thomson, John: Congenital Obliteration of the Bile-ducts, *Edinburgh Med. Jour.*, 1892, **37**, 523, 604, 724.

<sup>2</sup> Milne, L. S.: Congenital Atresia of the Bile Passages, *Quart. Jour. Med.*, 1911-1913, **5**, 409.

<sup>3</sup> Foote, J. and Hamilton, R.: Congenital Occlusion of Bile-ducts, *Am. Jour. Obst.*, 1916, **74**, 521.

<sup>4</sup> Frensdorf, W.: Ein Beitrag zur Kasuistik und Pathogenese des Kongenitalen Gallengangsatresien, *Monograph*, Wiesbaden, 1911.

<sup>5</sup> Merle, E. and Petit: Obliteration congenitale avec arret de developpement des voies biliaires par angiocholite, *Bull. Soc. anat. de Paris*, 1910, **85**, 29.

<sup>6</sup> Feldman, W. M. and Lawson, M. A.: *Lancet*, 1924, **ii**, 113.

On palpation the liver is felt to be enlarged and firm. The spleen also may often be felt. Vomiting is variable. Constipation is the rule. Emaciation gradually supervenes because of the disturbance in digestion, particularly of the fats. Niemann<sup>1</sup> studied the digestion in one case that lived for four months. He found a nitrogen absorption of from 80 to 93 per cent and a fat absorption of from 28 to 39 per cent. On a very low diet more fat was found to be excreted than was given to the child. Thus the nitrogen metabolism was normal and the fat metabolism greatly disturbed. The usual percentage of fat absorption is from 88 to 96 per cent. In most cases life does not extend beyond six months.

**Differential Diagnosis.**—In the differential diagnosis the principal conditions to be distinguished from congenital obliteration of the bile-ducts are congenital syphilis, icterus neonatorum and the grave forms of icterus of infants, which are sometimes known as Buhl's disease, Winckel's disease, etc. The history and the Wassermann test will serve to distinguish the former condition. The clay-colored stools will rule out the latter conditions.

### CONGENITAL CYSTS OF THE EXTRA-HEPATIC BILE-DUCTS.

Closely allied to the condition of congenital obliteration of the bile-ducts are the cystic dilatations of the extra-hepatic bile-ducts, which are supposedly of congenital origin. The most complete study of this condition is that by McWhorter<sup>2</sup> who in 1924 was able to collect 47 cases from the literature in addition to his own, which is admirably described. (Fig. 83.) The pathogenesis of this remarkable condition is not clear. By most of those who have described cases it is thought that the explanation of its origin lies either in one or both of two factors—a congenital partial obstruction of the lower end of the duct or a congenital weakness of the wall above. The partial obstruction in some cases has seemed to be due to an actual narrowing of the lumen, a valve formation, or to a sharp kink or angle at the junction of the duct with the duodenum. In 6 cases no apparent cause was found to explain the failure of emptying of the duct. In only 1 of the 48 cases was it definitely established that there was no lumen at all. In practically all cases the cystic dilatation has involved the middle and upper part of the choledochus, and the spherical sac of the cyst has been sharply

<sup>1</sup> Niemann: Der Verhalten des Stoffwechsels bei angeborenen Verschluss der Gallenwege, *Ztschr. f. Kinderheilk.*, 1912, **4**, 152.

<sup>2</sup> McWhorter, G. L.: Congenital Cystic Dilatation of the Common Bile-duct; Report of a Case, with Cure, *Arch. Surg.*, 1924, **8**, 604.



demarcated at the junction of the cystic and hepatic ducts. These ducts too are usually dilated but are distinct from the sac itself. The size of the cyst has varied from that of an adult fist to the size of a full-term fetus. The contents have usually been clear bile. Small calculi have been found frequently both in the sac and in the dilated ducts. In about one-third of the cases the gall bladder was dilated; in the others it was either normal in size or smaller than normal. The liver in about one-half the cases presented no noteworthy changes from the normal. In 14 cases a cirrhosis was said

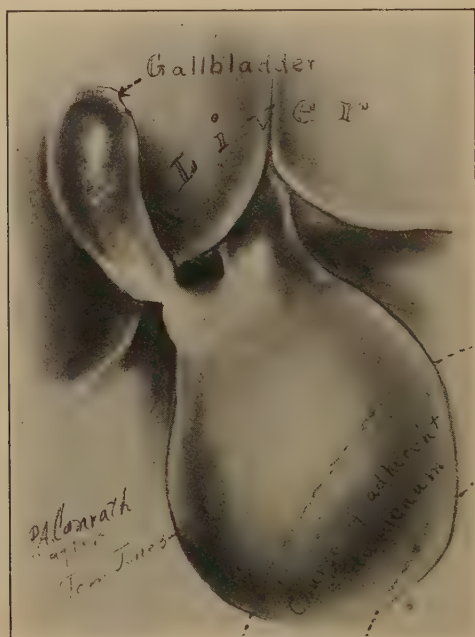


FIG. 83.—Dilatation of bile-duct. (After McWhorter.)

to be present, which was characterized as of a biliary type in 9 cases. In a few cases the liver was greatly enlarged. The contrast of the infrequency of hepatic cirrhosis in this condition as compared with its nearly constant presence in cases of congenital obliteration of the bile-ducts would seem to indicate that the pathogenesis of the two conditions is probably different, and support is thereby lent to Rolleston's hypothesis of the origin of congenital obliteration of the bile-duct, as mentioned in the preceding section. In the majority of the cases in which a microscopic examination of the cyst was made it was reported that there was no epithelial lining. In

other cases it was stated that the fibrous wall showed no differentiation of structure. Ascites was present in 5 cases and edema of the legs in 3.

The characteristic symptoms were recurrent attacks of jaundice, abdominal pain in the region of the liver and a palpable cystic tumor developing during childhood or youth. The onset was acute in 6 cases, with only a few days' duration. In other cases, however, the duration of the symptoms had varied from six weeks to forty-nine years. The onset of symptoms occurred at the age of six months in 4 cases and under ten years of age in more than 50 per cent of the cases. There was a marked predominance of incidence in females; 41 females to 6 males. The jaundice was intermittent in 23 cases. In other cases it was continuous. The presence of acholic stools was noted in some cases and not in others. The pain in some of the cases, notably in McWhorter's, was excruciating and paroxysmal. A correct diagnosis was not made in a single case before operation or postmortem examination.

### ACUTE CATARRHAL ICTERUS.

There is a condition characterized by mild icterus, malaise and gastro-intestinal symptoms, which is usually designated as acute catarrhal icterus. This name has remained in the literature very largely because of the prevalent belief that the icterus is due to an obstruction of the lower end of the common bile-duct by a plug of mucus resulting from a gastro-duodenal catarrhal inflammation. The condition is included here in this section dealing with the bile-ducts merely because of this more common belief in its origin, which has just been expressed. Its pathogenesis will be discussed a little later.

The clinical picture usually described for this condition is somewhat as follows: It is most common during the first and second decades of life. During or after the course of a gastro-enteritis or of an acute respiratory infection, jaundice is noticed. The jaundice is usually not extreme and it may be mild. It is said that as a rule the staining of the urine with bile is noticed before any discoloration of the scleræ. The urine often contains both bile pigment and bile salts. There is a considerable amount of malaise and there is often some mental depression. Nausea and vomiting are not prominent. Rather marked loss of weight is likely to occur. Fever is slight, and the temperature may be subnormal. The pulse may be slightly increased at first, but during the stage of the

deepest jaundice it is usually slow, the classical *bradycardia* associated with jaundice. After a period of from about ten days to six weeks the icterus has cleared and the patient feels well again, although perhaps still under his normal weight. On physical examination, in addition to the points noted above, the liver may be found to be slightly enlarged and tender; and occasionally a distended gall bladder can be palpated. There is leukocytosis at first, often followed by a leukopenia. At the height of the jaundice there is said to be a relative increase of the lymphocytes and of the large mononuclears. Both the hemoglobin and the number of the red blood cells are diminished. According to McNee a biphasic reaction occurs with the van den Bergh test, indicating a combination of obstructive with toxic and infective types of jaundice. The condition sometimes occurs in epidemic form.

It is fairly evident that such a picture may be only a syndrome in which mild jaundice occurs and that it is probably not a distinct entity. In a recent article by Klemperer, Killian and Heyd<sup>1</sup> a critical review is made of the evidence for assuming that this syndrome is due solely to a catarrhal obstruction of the lower end of the common duct. Virchow<sup>2</sup> lent the great weight of his own opinion in favor of this view by stating that the anatomical findings in such cases were: (1) Swelling of the ostium of the common duct; (2) obstruction of its lumen by a whitish plug composed of epithelial masses; (3) sudden dilatation of the bile-stained common duct above its intestinal portion. In a condition so mild, as acute catarrhal icterus ordinarily is, it is obvious that there would be only scant opportunity for postmortem examination. Occasionally, however, opportunity for such examination has presented itself, notably, for example, in the case of Eppinger,<sup>3</sup> a death by suicide during the course of a clinically diagnosed acute catarrhal icterus. In this case, in addition to an extensive gastro-duodenal catarrhal inflammation, the papilla of Vater was swollen and the bile-ducts were filled with dark tenacious bile. The situation was complicated, however, by the fact that Eppinger also had an opportunity to perform postmortem examinations on 3 jaundiced and wounded soldiers who died of tetanus who belonged to a larger group of jaundiced soldiers who recovered. The inference was made that they

<sup>1</sup> Klemperer, P., Killian, J. A. and Heyd, C. G.: The Pathology of Icterus Catarrhalis, Arch. Path., 1926, 2, 631.

<sup>2</sup> Virchow, R.: Ueber das Vorkommen und den Nachweis des hepatogenen, Insbesondere des katarrhalischen Icterus, Virchow's Arch. f. path. Anat., 1864, 32, 117.

<sup>3</sup> Eppinger, H.: Zur Pathogenese des Icterus Catarrh, Wien. klin. Wchnschr., 1908, 21, 480.

all had acute catarrhal icterus. But in these 3 cases the livers showed a diffuse degenerative process with multiple small foci of necrosis. The question naturally arises, therefore, did these 3 patients belong to the category of acute catarrhal icterus? The same question can very properly be asked of most of the other post-mortem examinations which have been performed on supposed examples of this condition; and this question naturally leads up to the further query, is there such a pathological entity as acute catarrhal icterus? Klemperer, Killian and Heyd report a case of supposed catarrhal icterus in which a laparotomy was performed and a small piece of liver tissue was excised for microscopic examination. In this case the hepatic parenchyma showed various stages of cellular degeneration and disintegration, and there were areas of marked cell atrophy. Leukocytic infiltration around the necrotic cells was conspicuous. They conclude that the so-called "icterus catarrhalis" is not a pathological entity but that three forms can be differentiated: (1) Icterus due to obstruction of the common duct following gastrointestinal catarrh—true catarrhal jaundice; (2) icterus due to degeneration and multiple necrosis of the liver, hematogenous in origin; (3) icterus due to cholangitis, mostly of hematogenous origin. Probably many different kinds of bacteria are responsible for different cases. Bacilli of the colon—typhoid group have been regarded as the etiological agents in many cases. Epidemic icterus due to spirochetosis icterohæmorrhagica should always be thought of in epidemics of jaundice.

In conclusion it might be said that the idea of jaundice being caused by a mucus plug in the common duct seems to us untenable for several reasons. In the first place the finding of a mucus plug at postmortem examination or in any other way does not indicate necessarily that it has produced obstruction. If no bile is pouring down the duct because of intra-hepatic obstruction it is but natural to suppose that there will be nothing to wash out any mucus that might collect in the duct. Also it is difficult to see how any mucus plug could adhere to the walls of the duct with sufficient tenacity to withstand the pressure of the bile behind it, which amounts to about 150 cm. of bile pressure. Moreover, such anatomical evidence as there is at hand in this condition shows nothing comparable to the dilatation of the ducts above the obstructed level, such as is seen in unquestioned cases of obstruction. Finally also one might ask the pertinent question, what is it that finally loosens this tenacious plug to permit the overwhelming majority of these cases to recover? If the pressure of the bile behind it cannot loosen it during the first week, how can it do it in the fifth week?



**CHOLANGITIS.**

The bile passages, comprising the gall bladder and the ducts, both those within and those outside of the liver, are an anatomical and a physiological unit. An abundant lymphatic supply connects these various parts of the unit to each other. An inflammation of one part of this unit, therefore, is usually reflected to other parts, probably by way of the lymphatics, as in the case of inflammation elsewhere. A severe acute inflammation of the gall bladder is accompanied also by acute inflammatory changes which affect to a more or less degree the whole system of bile-ducts. Conversely also a severe acute inflammation of the ducts affects the gall bladder. On account of varying local conditions, however, the intensity of the inflammation in different parts of this unit is usually different. In chronic or in mild inflammations the effects on different parts of the unit will be less obvious. It is particularly important to realize that no serious inflammation of the ducts fails to have serious effects on the liver which are not limited to the ducts within the liver but involve also the hepatic parenchyma to a more or less extent. Cholangitis may appropriately be considered under a variety of headings, such as: (1) Calculous cholangitis; (2) non-calculous infective cholangitis; (3) cholangitis associated with malignant disease; (4) parasitic cholangitis, although there are no sharp divisions between the different groups. Thus, for example, calculous cholangitis may be associated with severe infection and even with a carcinoma.

**Calculous Cholangitis.**—Cholangitis associated with the presence of gall stones in the ducts is, from a surgical standpoint, probably the most important type. In this section will be discussed the purely mechanical effects of stones in the various ducts as well as the inflammatory aspects of the condition.

**Stone in the Cystic Duct.**—In a preceding chapter on the origin of gall stones the question of where they may be formed has been extensively discussed. It will be recalled that the evidence is not by any means overwhelming that even most of the gall stones are formed in the gall bladder. Certainly in many instances stones are undoubtedly formed in the intra-hepatic bile-ducts. Therefore, when a stone is lodged in the cystic duct it is by no means certain that it has been forced there from the gall bladder even if there are also stones in the gall bladder. Sweet has produced rather striking evidence that at least some gall stones are formed in the cystic duct and drop back into the gall bladder. At any rate, almost always

there are stones in the gall bladder when one is present in the cystic duct. This doubt as to whether a stone lodged in the cystic duct has been forced there from the gall bladder is of interest in connection with the symptoms.

The typical clinical picture produced by this condition is that of the so-called *biliary colic*, namely, a sudden onset of severe pain in the right upper quadrant of the abdomen. The pain may occur in severe paroxysms, with soreness remaining in the intermissions. It is often referred to the angle of the right scapula and to the region of the lower dorsal spine. The pain is often of the most agonizing character, and it is sometimes likened to a sensation as if the back were being broken. The paroxysms, unless relieved by morphine, usually continue for several hours. The pain is so severe that the patient often rolls on the floor in agony. Rolleston mentions a few instances in which sudden death has occurred during a paroxysm as if caused by the severity of the pain. In some cases, however, pain may not be a noteworthy feature, at least it may not occur in severe paroxysms and its onset may not be sudden. Nausea and vomiting are usually present. Tenderness and rigidity of the abdominal muscles are made out on palpation. Moderate fever and leukocytosis are present. Jaundice is observed only in those cases in which the inflammation has extended up to involve the liver to a considerable degree. It is similar in origin to that which has already been mentioned as occurring in association with acute cholecystitis. If the blocking of the duct is complete the gall bladder will become distended unless its wall is so scarred with fibrous tissue as to preclude distention. Rolleston states that reflex constriction of the vessels in the lungs, with rise of blood-pressure in the pulmonary artery, has been described and is supported by the experimental observation that irritation of the bile-duct induces a reflex constriction of the pulmonary vessels (François-Fränck and Arloing).

Early in the course of the condition the contents of the distended gall bladder are mucopurulent and bile-stained. Later the bile pigment disappears and the contents may be nearly pure pus. Still later, because of the continuous secretion of mucus, diluted at times probably by serous exudate, the gall bladder may become enormously distended, a condition then often called *hydrops*. The wall of the vesicle may become greatly thickened and fibrosed if the condition is sufficiently chronic. The mucosa frequently shows ulceration in the more acute phases of the condition, and the epithelium is greatly flattened, although rarely if ever absent.

Occasionally the stone ulcerates through the wall of the duct to become lodged outside. Sometimes also a fistula is established in this way between the duct and some other organ. At other times a diverticulum is formed at the site of the stone, probably as a result of a partial destruction and weakening of the wall by the pressure and inflammation produced by the presence of the stone. Scarring of the duct may also occur which may later occasion stricture.

The origin of the pain in these cases has aroused much discussion. By some it has been thought that the strong contractions of the gall bladder trying to force the stone out and along the duct are responsible for it. This idea might be considered possible by those who believe that the gall bladder is capable of strong contractions. But it seems untenable to those who think that the gall bladder is incapable of strong contractions. The evidence of the question of the possibilities of strong contractions of the gall bladder has been extensively discussed in the chapter on Physiology. Other possible explanations of the pain are contractions of the muscle of the duct itself around the stone, distention of the duct and finally the inflammation nearly always associated with the presence of a stone in the duct. The paroxysmal character of the pain is often of such a nature that one is tempted to think that it is produced by forcible contractions of the muscle of the duct as if the stone were being propelled along it with difficulty, but we are not aware of any certain evidence which supports this idea.<sup>1</sup> If, as some believe, atropine helps to relieve the pain in these cases, this observation would support the idea of muscular spasm. But we have never seen any striking effect produced by atropine on the pain. Also it is well known that distention of any of the hollow viscera is accompanied by pain, but it seems hard to understand how even sudden distention could occur in a manner to coincide with the paroxysms of pain experienced by the patient. It is almost a certainty, however, that inflammation of some degree is necessary in order to have pain from a stone. In the absence of any positive evidence, one is forced to conclude that the origin of the pain cannot be satisfactorily explained at the present time. The pain often suddenly stops in a dramatic manner. The usual explanation of this event is that the obstructing stone has suddenly either dropped back into the gall bladder or has passed into the common duct.

<sup>1</sup> Peristaltic contractions of the common duct have been observed frequently in birds. See, for example, an article by Copher and Illingworth (*Mechanism of Emptying of the Gall Bladder and Common Duct*, Surg., Gynec. and Obst., 1928, in press.)

From a clinical standpoint the diagnosis of a stone impacted in the cystic duct apart from the more general diagnosis of biliary colic is only of academic interest except in those cases in which a mucous fistula has followed the surgical drainage of the gall bladder and except at the time when the surgeon at laparotomy is confronted with a distended organ. The conditions most commonly confused with biliary colic are renal colic, acute peritonitis from various causes, cardiac lesions, etc., which have been discussed in connection with the section on Acute Cholecystitis. But if a greatly distended gall bladder can be palpated through the abdominal wall, especially if there has been an antecedent history suggestive of cholecystitis or of biliary colic, the diagnosis of impacted stone in the cystic duct becomes almost certain. Uncertainty is often experienced, however, in determining whether the mass that is felt is a distended gall bladder or some other organ. Tumors and even displacements of the right kidney are conditions which are particularly likely to be confused with a hydrops of the gall bladder. A distended gall bladder usually shows some mobility from side to side and in a vertical direction on deep respiration, but it is generally not so easy to displace the gall bladder forward by palpation in the loin as in the case of a kidney tumor. Tumors of the liver, a Riedel's lobe of the liver, and tumors of the hepatic flexure of the colon all may be mistaken for a hydrops of the gall bladder. Obstruction of either the cystic or common ducts by a tumor, particularly a carcinoma of the pancreas with obstruction of the common duct, may produce a marked distention of the gall bladder which clinically may be confused with a hydrops from a stone in the cystic duct.

The presence of stones in the cystic duct does not necessarily imply that the duct has been obstructed. Hydrops is a result of obstruction and not merely of the presence of a stone in the duct. Not infrequently one encounters one or more stones in the cystic duct at operation without any distention of the gall bladder. These are of course cases in which no obstruction is present. It is common to find in such cases that the gall bladder is greatly fibrosed and shrunken, often with several stones in its lumen.

The stone or stones may be in any part of the duct, but the most frequent sites for impaction are at either end.

A case of hydrops of the gall bladder in an infant, sixteen months old, together with a review of the literature of hydrops in children is given in an article by Milch.<sup>1</sup>

<sup>1</sup> Milch, H.: Hydrops of the Gall Bladder in an Infant, *Ann. Surg.*, 1926, **84**, 415.



**Stone in the Common Duct.**—The frequency of stone in the common duct as shown in the figures given by Courvoisier<sup>1</sup> from postmortem records at the Basle Pathological Institute is 3.9 per cent of all cases of gall stones and 0.4 per cent of all postmortem examinations in a series of 2520 bodies examined. As regards the most common locations of stones in the common duct, there is a good deal of difference of opinion. Courvoisier found in 123 cases that the calculi were present throughout the whole common duct in 26; in the upper portion in 17; in the middle segment in 19; close to the duodenum in 20; in the orifice of the biliary papilla in 41. In almost one-half the cases the stone was close to the lower end of the duct. In 380 cases Mayo Robson,<sup>2</sup> found the stone to be at the duodenal end in 67 per cent, in the middle portion in 18 per cent, and at the upper end in 15 per cent. Vautrin,<sup>3</sup> however, in 47 cases found calculi in the part of the duct above the duodenum in 27, in the part in contact with the duodenum in 18, and in the ampulla of Vater in 2 cases. These figures would agree more closely with our own experience than the preceding ones. The number of stones which may be found in the common duct is subject to great variation. In some cases both hepatic ducts and the common duct are plugged with a soft, clay-like material which resembles putty very closely both in appearance and in consistency. In other cases there are many faceted stones, and in still others there may be a single, spherical stone. In the majority of cases there are stones in the gall bladder also.

**Pathology.**—The pathological changes produced by stone in the common duct are essentially of two kinds, those due to the concomitant inflammation and those due to obstruction. This condition is almost always associated with a chronic cholecystitis, and for that reason the gall bladder is usually fibrosed and contracted. In a study of 87 cases of calculous obstruction of the common duct Courvoisier found the gall bladder shrunken in 70 cases, 80.4 per cent, and distended in 17 cases, 19.6 per cent. On the other hand, in 100 cases of obstruction of the duct by other causes, he found that in 92 the gall bladder was distended and in only 8 was it shrunken. Because of these findings he announced his now famous conclusion which is often called *Courvoisier's*<sup>4</sup> law, namely: "with obstruction of the choledochus by stone, distention of the gall bladder is rare;

<sup>1</sup> Courvoisier, L. G.: *Casuistisch-statistische Beiträge zur Pathologie und Chirurgie der Gallenwege*, 1890, Leipzig, Vogel, p. 43.

<sup>2</sup> Mayo Robson: *Diseases of the Gall Bladder and Bile-ducts*, 1904, p. 278.

<sup>3</sup> Vautrin: *Rev. de Chir.*, 1896, p. 454.

<sup>4</sup> Courvoisier: *Loc. cit.*, p. 58.

the organ is usually shrunken. With obstruction of other kinds, on the contrary, distention is the rule; shrinking occurs in only one-twelfth of these cases." The common duct, and generally all the ducts, show the effects of chronic inflammation by fibrosis of the walls. Benign stricture of the duct occurs sometimes as a late effect of the inflammatory disturbances found associated with calculous choledochitis, but fortunately it is a rare complication. Occasionally the stone ulcerates through the wall of the duct, and fistulae sometimes develop between the duct and other viscera. Because of the pericholangitis often present, the foramen of Winslow may be obliterated. Carcinoma of the duct, or of the papilla of Vater is occasionally found accompanying a stone in the duct. In those cases in which obstruction of the duct has been present for a long time, there is usually a marked dilatation above the obstruction so that the duct not uncommonly is large enough to admit a finger into its lumen, and sometimes it is so large that it resembles small intestine. This effect is also seen to extend backward to involve the liver. Not only are the intrahepatic ducts often much enlarged but the chronic inflammation of the liver itself often results in the production of a biliary cirrhosis, a condition in which, because of an extensive pericholangitis, fibrous tissue is formed in excessive amounts around the ducts which despite their thickened walls are usually dilated. The liver, although large in the early stages, becomes smaller than normal, and of a dark-green color; and it has an irregular surface between which and the diaphragm there may be many adhesions. It cuts usually with less resistance than does the liver in a case of ordinary atrophic cirrhosis, and if obstruction has been of long-standing a section through it gives a peculiar honeycombed appearance because of the numerous dilated ducts. There may be marked atrophy of the liver lobules and areas of focal necrosis. Rolleston points out several respects in which the changes in the liver associated with calculous obstruction of the common duct are different from those observed in hypertrophic biliary cirrhosis. In the latter the ducts are not dilated; and even the finest intra-hepatic ducts show a pericholangitic fibrosis, while in calculous obstruction the finest ducts usually show little or no change. Also in hypertrophic biliary cirrhosis the parenchymatous cells show much less change than in the other condition. Rolleston has also considered in great detail the question of how much the mechanical factor of biliary obstruction plays a part in the production of biliary cirrhosis, and he comes to the conclusion that it is of minor importance. We are inclined to agree with him because

we have seen extreme examples, of the type of cirrhosis ordinarily encountered in calculous obstruction of the common duct, in patients with severe chronic calculous cholecystitis who presumably had never had any biliary obstruction because they had never had jaundice. The type of hepatitis which has been observed by one of us (Graham<sup>1</sup>) as occurring almost uniformly in association with cholecystitis is of a kind which would produce the pericholangitic kind of fibrosis discussed above. In enumerating the various ways by which such a fibrosis can occur we feel that Rolleston, however, has omitted one very important pathway, the lymphatics, which are known to extend upward into the liver around the bile-ducts. These form a very accessible route by which infection from any part of the extra-hepatic biliary apparatus can reach the liver. (See in this connection the section on the Pathogenesis of Cholecystitis.) If an acute infection has supervened on the chronic one multiple abscesses of the liver may be found of the type which will be described later in connection with non-calculous cholangitis.

The spleen is often of normal size or even smaller than normal. But in cases with marked fibrosis of the liver it is commonly enlarged.

The pancreas, in cases of calculous choledochitis, shows changes of various kinds. It is a common experience of surgeons while operating on a case of chronic cholecystitis or of stone in the choledochus to note that the pancreas feels harder than normal and that its head is considerably enlarged. Often this portion of the organ is so hard that the opinion is formed that a carcinoma is present. More commonly, however, the abnormal condition is due to an interstitial pancreatitis than to malignant disease. In very chronic cases the pancreas is smaller than normal and much fibrosed. The atrophy, however, is usually at the expense of the acini, and the islands of Langerhans, which produce insulin, are but little affected. In spite of the fact that chronic pancreatitis is not rare in cholelithiasis, it has been an old observation that the incidence of diabetes in cases of gall-bladder disease is not appreciably greater than in those without. The work of Tedstrom, Bond, Olmsted and Moore,<sup>2</sup> who used the newer method of cholecystography in a study of a series of diabetic patients, is in conformity with the generally accepted view in that regard. The enlargement of the head is of course usually not due to fibrous tissue but to swelling, and the subsidence of infection

<sup>1</sup> Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, Surg., Gynec. and Obst., 1918, **26**, 521.

<sup>2</sup> Tedstrom, M. K., Bond, R. C., Olmsted, W. H. and Moore, S.: Cholecystography in Diabetes Mellitus, Jour. Am. Med. Assn., 1926, **87**, 1603.

in the duct often results in the subsidence of the swelling of the pancreas. Pratt<sup>1</sup> is inclined to think that this swelling of the pancreas does not occur with the comparative frequency which the surgeons think. A discussion of the matter will be found in his article. When a calculus is lodged in the pancreatic portion of the common duct it is sometimes confused at operation with a chronic pancreatitis or with a carcinoma of the pancreas. Opie<sup>2</sup> in 1901 described a case of acute necrosis of the pancreas, a condition often called acute hemorrhagic pancreatitis, in which at autopsy a gall stone was found lodged in the ampulla of Vater in such a way that there was a complete obstruction of bile. As a result of this blocking it seemed apparent that bile had been forced up the duct of Wirsung into the pancreas and had been responsible for the production of the acute necrosis of this organ. He<sup>3</sup> later found other cases which had apparently been produced by the same mechanism. Since that time this idea has received much attention. Although it is probable that in some cases the explanation of the acute pancreatic necrosis may be found in the blocking of the ampulla or of the orifice of the papilla of Vater by a stone, yet this mechanism cannot account for all cases because in the majority of instances no gall stones are present. Egdahl,<sup>4</sup> for example, in 105 collected cases of the condition found that in only 44 cases were gall stones actually found or suspected. Other theories of the origin of the condition are discussed in the section on the Pathology of Cholecystitis.

*Clinical Features.*—The most striking clinical expressions of a stone in the common duct are attacks of biliary colic followed by jaundice. Usually there is a long antecedent history of symptoms suggestive of chronic cholecystitis with perhaps even a definite history of biliary colic followed by only slight if any jaundice. Finally, however, an attack of unusually severe pain occurs, and the patient discovers a day or two later that he is markedly jaundiced. The typical features of biliary colic have already been described above in connection with stone in the cystic duct. The degree of jaundice is variable, depending upon the completeness of the obstruction of the bile-flow. It is important to realize of course that the biliary obstruction may not be due solely to a mechanical block-

<sup>1</sup> Pratt, J. H.: Diseases of the Pancreas, Oxford Med., vol. 3, part I, p. 473.

<sup>2</sup> Opie, E. L.: The Etiology of Acute Hemorrhagic Pancreatitis, Bull. Johns Hopkins Hosp., 1901, 12, 182.

<sup>3</sup> Opie, E. L.: Disease of the Pancreas; its Cause and Nature, 2d ed., Philadelphia, J. B. Lippincott, Company 1910.

<sup>4</sup> Egdahl, A.: A Review of One Hundred and Five Reported Cases of Acute Pancreatitis, with Special Reference to Etiology; with report of Two Cases, Bull. Johns Hopkins Hosp., 1907, 18, 130.



ing of the lumen of the duct by the stone. It is probably always in part produced by inflammatory swelling of the duct, and this swelling may not be confined to the common duct itself but may also be an expression of the effects of the associated inflammation on the finer bile passages within the liver. It is perhaps also in part due to toxic and inflammatory effects on the parenchymatous and reticulo-endothelial cells of the liver, in accordance with the more recent ideas of McNee and others on the origin of jaundice. The course of events is probably somewhat as follows: A stone becomes lodged in the duct and an inflammatory process is set up. This extends to involve the whole system of ducts. The outflow of bile is blocked, partially or completely as the case may be. Gradually the inflammatory swelling subsides. During this time the position of the stone may have changed also so that it no longer acts as a plug. Osler<sup>1</sup> in 1881 and Fenger<sup>2</sup> in 1896 both called attention to the possibility of the stone acting like a ball-valve, sometimes floating up in the bile a little so that some of it can escape. At the site of impaction of the stone the duct usually also becomes somewhat dilated, thus facilitating the passage of bile around the stone after the edema has subsided. All of these elements may play their respective rôles in the reëstablishment of the flow of bile, at least in some degree. It is not surprising, therefore, to find that the jaundice in cases of calculous choledochitis is nearly always temporary rather than permanent. Its duration depends upon the duration of the obstruction. It is also recurrent. With another attack of biliary colic it is very likely to occur again. It is a remarkable fact that a stone may remain latent in the common duct for years between attacks of biliary colic and of jaundice. There is much evidence to support this. In our own experience, one of us has seen a case in which after a severe attack of pain intense jaundice developed lasting for two weeks. This was followed by an interval of eight years before another attack of pain or jaundice occurred. At operation a single non-facetted calculus, about the shape and size of an olive stone, was found in the common duct. The gall bladder was markedly fibrosed and atrophic and contained no other stones. The presumption was strong, therefore, that this stone had remained dormant in the common duct during this long interval of eight years. It is not known with certainty how much mechanical

<sup>1</sup> Osler, W.: On Some of the Effects of the Chronic Impaction of Gall Stones in the Bile Passages, and on the "fièvre intermittente hépatique" of Charcot, *Med. Times and Gaz.*, 1881, **2**, 111, quoted from Rolleston.

<sup>2</sup> Fenger, C.: Stones in the Common Duct and their Surgical Treatment, *Am. Jour. Med. Sci.*, 1896, **111**, 125.

factors participate in starting an attack of biliary colic. In some cases the attack has followed immediately after violent exercise, but in many cases it has begun at night while the patient was asleep. Probably inflammation plays a more important rôle in inaugurating the colic than simple mechanical movement of the stone.

Obstructive jaundice usually reveals itself first in a discoloration of the scleræ. Later the skin of the entire body becomes yellow, and if the obstruction is complete it may become a dark brown with a suggestion of a greenish tinge. It is notorious that the early yellow shades of jaundice, plainly seen in daylight, are not discernible in artificial light. The discoloration is not confined to the skin but affects also the mucous membranes and in fact all the organs and tissues of the body. The urine becomes dark brown because of its content of bile pigment and it usually contains casts and some albumen. Due to the absence of bile in the intestine the feces are light-colored; and if they contain a large amount of undigested fat they may be white or of a light-clay color. Itching of the skin is a common complaint. Patients who have had a long-standing jaundice will generally reveal numerous scratch marks. The pulse is often slower than normal (*bradycardia*). Mental disturbances are not uncommon, a fact from which possibly the idea of the melancholia arose in Hippocrates's humoral theory of disease. There is also a well-known tendency of jaundiced patients to bleed easily. The clotting time is often much prolonged; but frequently even when the clotting time is found to be within normal limits, as judged by all the available methods of examination, bleeding still is found to continue well beyond the normal time. For that reason estimations of the bleeding time are important, particularly when an operation is contemplated. This feature is given special consideration in the chapter on Treatment. Loss of weight may be rapid because of failure to digest fats properly.

With a stone in the common duct a patient is very likely to display a group of symptoms first described by Charcot<sup>1</sup> and since that time often referred to as *Charcot's intermittent hepatic fever*. Osler<sup>2</sup> has also strongly emphasized these symptoms. Presumably they are associated with the type of calculus which acts like a ball-valve, mentioned above. The most striking clinical feature of this con-

<sup>1</sup> Charcot, K. M.: *Leçons sur les Maladies du Foie et des Voies Biliaires*, 1877, p. 178.

<sup>2</sup> Osler, W.: *Fever of Hepatic Origin, Particularly the Intermittent Pyrexia Associated with Gall Stones*, *John Hopkins Hosp. Rep.*, 1891, 2, 3.

dition is the recurrence of attacks of intense pain, chills, fever and increase of jaundice, following intervals of moderately good health and comfort, during which the patient is often able to lead a normal life. In most cases, however, during the intervals the patient remains slightly jaundiced. The attacks come on suddenly and sometimes resemble malaria because of their striking periodicity and the presence of chills, which may be as severe as those occurring in malaria. The temperature frequently reaches 103° F. and may go higher. Sweating is common. The pain of biliary colic is present. The liver is usually slightly enlarged and tender; and the spleen is often palpable. The jaundice deepens soon after the attack. Leukocytosis (15,000 to 20,000) is present during the attacks, but not in the intervening periods of comparatively good health.

Recent work of Brakefield and Schmidt<sup>1</sup> indicates that liver injury may result from even uncomplicated biliary stasis. They found that biliary obstruction is followed by urinary excretion of bile acid as well as bile pigment. The output of bile acid gradually decreased to a small quantity, while there was a fairly constant level of excretion of biliary pigment. They believe that the decreased output of bile acids during jaundice due to obstruction argues for the impairment of the function of the liver.

An immediate rise in the bilirubin content of the blood after ligation of the common bile-duct and extirpation of the gall bladder was found by Bollman.<sup>2</sup> A gradual and continued increase in the content of the bile pigment in the blood followed for several hours after the obstruction of the duct. Obstruction of the biliary ducts was followed by a rapid rise of pressure in the ducts above the obstruction. This rise of pressure was found to be modified by the presence or absence of a gall bladder which is able to concentrate its content. Bollman believes, when the pressure in the ducts has risen to from 250 to 300 mm. of water, that the hepatic cell is unable to excrete pigment into the bile capillaries or absorb it from the blood. As a result of this mechanism there results an obstructive jaundice.

*The association of jaundice with a tendency to bleed easily* has long attracted attention and aroused discussion. The same tendency was long ago found to be present in certain conditions in which the liver was known to be damaged, particularly in phosphorus poison-

<sup>1</sup> Brakefield, J. L. and Schmidt, C. L. A.: Studies on the Synthesis and Elimination of Certain Bile Components in Obstructive Jaundice, Jour. Biol. Chem., 1926 **67**, 523.

<sup>2</sup> Bollman, J. L.: An Experimental Study of Obstructive Jaundice, Proc. of the Staff Meetings of Mayo Clinic, 1927, **2**, 24.

ing. The natural conclusion therefore was drawn that the explanation of the bleeding was the same in both cases. In 1905 Doyon,<sup>1</sup> later with Gautier, Kareff and Morel, produced evidence which strongly suggests that fibrinogen is formed chiefly in the liver, and that interference with normal liver functioning interferes correspondingly with the production of fibrinogen and therefore induces a condition of diminished coagulability of the blood. Whipple and Hurwitz,<sup>2</sup> from experiments dealing with chloroform intoxication, later arrived at the same general conclusions. Morawitz and Bierich<sup>3</sup> concluded that the prolonged coagulation time in cases of cholemia is due to a delayed formation of fibrin ferment, which they thought was due to a diminution or absence of thrombokinase. They regarded the alteration in the coagulation time as independent of the presence of bile salts in the blood and as having no relationship to the duration or intensity of the jaundice. King and Stewart<sup>4</sup> found that in obstructive jaundice the calcium content of the blood is increased and proposed that in icterus the calcium might be combined with bilirubin and biliverdin as a protective mechanism against the toxic effect of these bile pigments. King, Bigelow and Pearce<sup>5</sup> found that in obstructive jaundice there is an increased calcium content in the blood, liver and kidneys, and they suggested that the prolonged coagulation time may be due to a binding of the calcium to the bile pigments in such a way that it is not promptly available for the process of clotting. Lee and Vincent<sup>6</sup> made an important contribution to this subject in 1915. They found from observations on both patients and on experimental animals that obstructive jaundice in the presence of a liver which is functioning in an adequate manner causes a delay in the coagulation time of the blood, but that the maximum effect on the clotting time does not appear until about five weeks after the obstruction. This condition must be differentiated from certain somewhat similar conditions in which the liver itself is seriously damaged. The delay in the coagulation of the blood in obstructive jaundice is apparently due

<sup>1</sup> Doyon: *Jour. de physiol. et de path. gen.*, 1905, **7**, 639; *ibid.*, 1910, **12**, 197; *ibid.*, 1906, **6**, 227; *ibid.*, 1906, **8**, 783; *ibid.*, 1906, **8**, 1003; *ibid.*, 1907, **9**, 405.

<sup>2</sup> Whipple, G. H. and Hurwitz, S. H.: Fibrinogen of the Blood as Influenced by the Liver Necrosis of Chloroform Poisoning, *Jour. Exper. Med.*, 1911, **13**, 136.

<sup>3</sup> Morawitz, P. and Bierich, R.: Ueber die Pathogenese der cholämischen Blutungen, *Arch. f. exper. Path. u. Pharmacol.*, 1907, **56**, 115.

<sup>4</sup> King, J. H. and Stewart, H. A.: Effect of the Injection of Bile on the Circulation, *Jour. Exper. Med.*, 1909, **11**, 673.

<sup>5</sup> King, J. H., Bigelow, J. E. and Pearce, L.: Experimental Obstructive Jaundice, *Jour. Exper. Med.*, 1911, **14**, 159.

<sup>6</sup> Lee, R. I. and Vincent B.: The Relation of Calcium to the Delayed Coagulation of Blood in Obstructive Jaundice, *Arch. Int. Med.*, 1915, **16**, 59.



to a lack of available calcium in the blood and can be counteracted by the administration by mouth of calcium salts. They devised a simple test by which the need of more calcium can be demonstrated at the bedside. They called this the "calcium *in vitro*" test. In performing the test some of the patient's blood is first examined by one of the ordinary methods for determining the clotting time. Then a second determination is made by adding to 1 cc. of blood 3 drops of a 1 per cent solution of calcium chloride. If there is need of calcium, the blood in the second test clots much more rapidly than in the first. In one case, for example, the clotting time of the blood as it came from the patient was thirteen minutes and in another sample, to which calcium was added, it was five minutes. Their studies also seemed to show that while the effect of bile in delaying coagulation is largely counteracted by calcium, yet bile has in addition an inhibitory effect on the formation of thrombin and on the action of thrombin already formed. Moreover, bile in very strong concentration *in vitro* entirely prevents coagulation even in the presence of an excess of calcium. It is to be doubted, however, if in obstructive jaundice such concentration of bile ever occurs as will entirely prevent the coagulation of blood. Clinically this need of calcium can be met by the administration of any soluble calcium salt. They used chiefly calcium lactate in the dose of 100 gr. (6.48 gm.) a day. It is necessary to administer calcium over a period of several days before any marked effect on the coagulation time is seen. The necessity of employing large doses depends on the difficulty of securing the absorption of calcium from the gastrointestinal tract rather than the need of such large amounts of calcium. In a dog, they found that prompt effect on the coagulation time could be obtained by the intravenous injection of calcium salts in solution. Apparently calcium can be given in this way without bad results, but its effect on the coagulation of the blood is transitory. Walters<sup>1</sup> and later Walters and Parham<sup>2</sup> have confirmed these findings in a considerable number of patients, and they report therapeutic results as equally striking as those of Lee and Vincent.

As possibly bearing on the matter of a hemorrhagic tendency in those cases with more or less serious impairment of liver function, in which it might be supposed from the work of Doyon and others mentioned above that there is an inability to form a proper amount

<sup>1</sup> Walters, W.: Preoperative Preparation of Patients with Obstructive Jaundice, Surg., Gynec. and Obst., 1921, **33**, 651.

<sup>2</sup> Walters, W. and Parham, D.: Renal and Hepatic Insufficiency in Obstructive Jaundice, Surg., Gynec. and Obst., 1922, **35**, 605.

of fibrinogen, the protective action of liver glycogen should be mentioned. Roger<sup>1</sup> long ago recognized the detoxicating action of the liver against strychnine. Since then it has been learned that the liver exercises a similar action against many other poisonous substances, and that this protective property of the liver is chiefly dependent on glycogen. Rosenfeld<sup>2</sup> has shown that animals fed upon carbohydrates are in general less susceptible to all those drugs which produce fat accumulation in the liver. These same drugs are also capable of producing a tendency to excessive bleeding, such as chloroform, phosphorus, etc. One of us (Graham<sup>3</sup>) has shown that the resistance of young pups to late chloroform poisoning, or chloroform necrosis, a condition in which one often finds multiple hemorrhages, is due to the high glycogen content of their livers, and that generous feeding of sugar to adult dogs renders them much less susceptible to these same late poisonous manifestations of chloroform because it enables the liver to contain that much more glycogen. Beddard<sup>4</sup> long ago suggested that patients who were to receive a chloroform anesthesia should be previously given a generous allowance of carbohydrate. Opie and Alford<sup>5</sup> also found that in mice the feeding of carbohydrates exerts a decidedly protective action against the development of liver necrosis by chloroform. Rosenbaum<sup>6</sup> had already shown as early as 1882 that after a protracted chloroform narcosis the liver is actually poor in glycogen.

*Diagnosis.*—In a typical case of stone in the common duct characterized by repeated attacks of biliary colic followed by deep jaundice, chills and fever, the diagnosis is easy. When these characteristic features are present the clinical diagnosis will be accurate in nearly 100 per cent of cases. In cases of obstruction of the duct by malignant disease, the most characteristic clinical features are the insidiousness of the onset and the fact that the jaundice is progressive instead of intermittent. Pain also is much less prominent in malignant disease than in calculous obstruction. In some cases the two conditions coëxist with the result that the clin-

<sup>1</sup> Roger, G. H.: Action du foie sur la strychnine, Arch. de physiol. norm. et path., 1892, **4**, 24.

<sup>2</sup> Rosenfeld, G.: Fettbildung, Ergebn. d. Physiol., 1903, **2**, pt. I, 50.

<sup>3</sup> Graham, E. A.: The Resistance of Pups to Late Chloroform Poisoning in its Relation to Liver Glycogen, Jour. Exper. Med., 1915, **21**, 185.

<sup>4</sup> Beddard, A. P.: A Suggestion for Treatment in Delayed Chloroform Poisoning, Lancet, 1908, **i**, 782.

<sup>5</sup> Opie, E. L. and Alford, L. B.: The Influence of Diet on Hepatic Necrosis and Toxicity of Chloroform, Jour. Am. Med. Assn., 1914, **62**, 895.

<sup>6</sup> Rosenbaum, F.: Untersuchungen über den Kohlehydratbestand des tierischen Organismus nach Vergiftung mit Arsenik, Phosphor, Strychnin, Morphinum, Chloroform, Arch. f. Exper. Path. u. Pharmacol., 1882, **15**, 450.

ical picture is much confused. For example, there may be complete malignant obstruction and yet also severe biliary colic because of inflammation in the duct kept up by the presence of calculi. Cases of calculous cholecystitis with cholangitis extending up into the liver causing jaundice often resemble the picture of stone in the common duct so closely that a differentiation can be made only at operation. Those cases in which the intermittent hepatic fever is conspicuous are sometimes confused with malaria, but the leukocytosis, the absence of parasites in the blood and a long-standing history of symptoms suggestive of disease of the biliary tract should serve to clear the confusion. The various cirrheses of the liver are also sometimes mistaken for common-duct stone, but usually there is little likelihood of confusion.

There is one type of case of which the features are rather characteristic and in which it is important to establish a diagnosis. If, after a cholecystectomy for calculous cholecystitis, the patient has attacks of biliary colic with intermittent jaundice and fever, it is almost certain that he is suffering from a stone in the common duct which was overlooked at the former operation. Stricture of the duct from scar tissue will often give a clinical picture closely resembling that of stone. If the symptoms are due to a stricture following an injury to the duct in an operation of cholecystectomy there will usually be obtained a history of a profuse discharge of bile after the operation. In hemolytic jaundice the discoloration is not so intense, bile pigment is not found in the urine, there is likely to be little or no pain, and there is an increased fragility of the red blood cells. As a part of the diagnosis of stone in the common duct it is important to test the coagulation time of the blood, especially before operation. The roentgen-ray usually is of little help in making a diagnosis of stone in the common duct except insofar as cholecystography will reveal an abnormal gall bladder and for that reason will focus attention more certainly on the biliary tract as the cause of the trouble. In any case it is important to rule out the possibility of an acute intoxication with liver damage. The syndrome known as acute yellow atrophy is often mistaken for common-duct stone. In this condition the pain is less severe, the mental symptoms greater, the prostration more marked, the liver is small and there are crystals of leucin and tyrosin in the urine. We have seen 2 cases of salvarsan poisoning mistaken for common-duct stone, and in 1 case an operation was performed.

**Stone in the Hepatic Ducts.**—As has been noted above, it is fairly common to find stones situated all along the extra-hepatic biliary

passages. Likewise it is not a rare occurrence for stones to be found inside the intra-hepatic ducts. When in this location they are often called liver stones. It is rare, however, for stones to be located in the hepatic ducts alone. There are no clinical features which distinguish a stone in one of the hepatic ducts from a stone in the common duct.

**Non-calculous Infective Cholangitis.**—In this group of conditions one usually considers catarrhal icterus and suppurative cholangitis. Rolleston also described a chronic catarrhal cholangitis which should be included in this group. Catarrhal icterus has already been considered separately above for the reasons there given. *Suppurative cholangitis* is commonly associated with gall stones, but there are also other conditions both local and general which may predispose to it. Of the local conditions, the most important probably are the lowering of local resistance and the occurrence of obstruction or at least of stagnation of bile. It becomes evident therefore that not only calculi but also parasitic worms, carcinoma, etc., may produce those factors which are necessary to initiate a suppurative infection. So rare a condition as an aneurysm of the hepatic artery was even found by Osler and Ross<sup>1</sup> to have produced a fatal suppurative cholangitis. Of the general diseases found associated with the condition Rolleston mentions typhoid fever, pneumonia and influenza. It seems probable also that general wasting diseases would predispose to the condition in any cases in which the local conditions were suitable. Various bacteria such as *Bacillus coli*, *Bacillus typhosus* and *paratyphosus*, staphylococci, streptococci, pneumococci and occasionally even *Bacillus ærogenes capsulatus* have been found in association. All of the biliary-duct system is usually involved, including the gall bladder. The ducts are dilated with pus which is often bile-stained, and their walls are edematous and infiltrated with leukocytes. Pericholangitic suppuration is also very likely to be present. The liver is enlarged and soft from edema. Multiple abscesses are found which, before they have broken down, appear as yellowish-gray nodules suggesting carcinomatous metastases in their appearance. As softening progresses many of these abscesses coalesce to form larger ones. Those beneath the capsule sometimes perforate and cause peritonitis, which may be either local or general. The pus may spread also to involve the lesser peritoneal cavity. The neighboring lymph glands are swollen and contain pus. The portal vein is sometimes involved by

<sup>1</sup> Osler, W., and Ross, G.: Aneurism of Hepatic Artery; Multiple Abscesses of the Liver, *Canada Med. and Surg. Jour.*, Montreal, 1877, 6, 1.



extension with the added complication of a suppurative pylephlebitis, which in turn may give rise to more intra-hepatic abscesses. Empyema of the right pleural cavity has followed the condition, but it is a very rare complication because ordinarily the diaphragm is an effective barrier. Infection sometimes also extends into the pancreas and sets up a suppurative pancreatitis. Subphrenic abscess is not uncommon. Finally there may be a pyemia with abscesses scattered throughout the body.

The symptoms and signs of acute suppurative cholangitis are those of acute suppuration usually added to those of biliary obstruction. As might be expected, therefore, in a condition of such severe damage to the liver as is often found in these cases, the patient, in addition to having very severe chills and a high septic type of fever, shows marked prostration. Jaundice is usually constantly present, but there are cases in which slight intermittency of the jaundice occurs. The pulse is rapid. A high leukocytosis is generally present. Pain is a variable symptom. In some cases it is prominent, and in others it is slight or absent. If the condition is associated with cholelithiasis the pain is more likely to be severe, and there may be typical attacks of biliary colic. If peritonitis is present there may be pain from that source, as well as other symptoms such as nausea and vomiting, meteorism, rigidity of abdominal muscles, etc. The liver is usually enlarged and tender on palpation. The course of the usual case before death occurs is seldom more than a few weeks.

Two other conditions are especially difficult to differentiate clinically from acute suppurative cholangitis. These are amœbic abscess of the liver and suppurative pylephlebitis. In amœbic abscess, jaundice and pain are likely to be less prominent and there may be a local bulging of the chest wall from edema at a site where the abscess is threatening to perforate. There is usually a history of a preceding colitis with passage of mucus and bloody pus in the stools. Suppurative pylephlebitis is sometimes impossible to differentiate, and in fact the two conditions sometimes coexist. There is often, however, a demonstrable source for the infection in the portal system, such as a previous acute appendicitis. In pylephlebitis the jaundice is usually less pronounced than in suppurative cholangitis and there is less likely to be pain resembling biliary colic. In ordinary cases of calculous choledochitis the rigors and fever are much less conspicuous.

**Parasitic Invasion of the Bile-ducts.**—Intestinal parasites occasionally enter the bile-ducts from the duodenum. Of these the most common is *ascaris lumbricoides*, or roundworm. Rolleston

states that there are about 90 cases on record in which the bile-ducts have been invaded by this parasite. The effects produced by these worms are both mechanical and infective. Obstruction of the common or other ducts is frequent when one of these worms has entered the biliary tract. The clinical features are therefore very similar to those associated with stone in the duct which have been described above. The presence of a roundworm as the cause of the symptoms should be suspected in children who have biliary colic and roundworms or their ova in the stools. However, the diagnosis during life has been made only rarely. *Distomiasis* is seen chiefly in Orientals. Here again the effects and therefore the symptoms produced by these flukes are both mechanical and infective. *Hydatid* (*echinococcus*) cysts have not only been found in a few instances in the walls of the bile-ducts, but they have also been found to occupy the lumens of the ducts, which they have reached by the perforation of a hydatid cyst of the liver. *Coccidium cuniculi* and *poracephalus constrictus* have also been reported as having invaded the bile-ducts in a few cases.

### BENIGN STRICTURE OF THE DUCTS.

Benign strictures of the ducts are in general of two kinds, those due to inflammation alone and those due to injuries to the ducts. The essential pathology is blocking of the duct by scar tissue. At the site of the stricture the duct may show for a distance of 2 or 3 cm., or even more, complete replacement by a mass of hard fibrous tissue. The process of formation is probably essentially the same as that in the urethra or in any other similar channel. Before the stricture results in complete obstruction there is a tortuous canal which permits the passage of only a small amount of bile. Those examples of stricture which have been due only to inflammation have for the most part been associated with calculi, which probably have caused extensive ulceration of the duct. In some instances stones have been found embedded in the scar tissue. As a result of the obstruction various changes occur in the biliary tract above the stricture. Above the scar tissue the duct is usually dilated and the liver is engorged with bile and generally enlarged and somewhat softer than usual. However, because of extensive biliary cirrhosis that organ may not be much enlarged and may be firm. Intense icterus is almost always present. The intra-hepatic ducts may be much dilated. (Figs. 84 and 85.) This dilatation has been shown by Counsellor and McIndoe<sup>1</sup> in some striking preparations. By

<sup>1</sup> Counsellor and McIndoe: Dilatation of the Bile-ducts (Hydrohepatosis), Surg., Gynec. and Obst., 1926, 43, 729.

far the most frequent site of stricture is at the junction of the cystic and hepatic ducts. Less frequently are the right or left hepatic



FIG. 84.—Normal biliary tree showing slender branches, vasa aberrantia, and parietal sacculi. (After Counsellor and McIndoe.)



FIG. 85.—Cholelithiasis and choledocholithiasis; generalized dilatation. (After Counsellor and McIndoe.)

ducts or the choledochus involved alone. Stricture of the cystic duct also occurs, in which case there is no jaundice as the result of the stricture but there may be a hydrops of the gall bladder. As regards the frequency of the occurrence of spontaneous stricture in relation to that following operations on the biliary tract, Eliot<sup>1</sup> quotes statistics from the Mayo Clinic which showed that 18 of 38 cases had had no previous operations. Those strictures which occur as the result of injuries to the ducts are usually due to an accidental removal of a portion of the common hepatic duct during a cholecystectomy. Such accidents should be avoided by exercising great care in securing a proper exposure of the anatomical relationships of the cystic and common ducts. If a section of the common duct has been accidentally removed the fact can be recognized at the time by the escape of bile from the open end of the duct and also by seeing two lumens in the removed tissue instead of the single one representing the cystic duct.

The clinical features of stricture involving the common or hepatic ducts closely simulate those of stone in the respective ducts. There are attacks of biliary colic which sometimes are severe; and the jaundice may be intermittent, although generally it does not clear entirely but merely becomes less intense during the intermissions between the attacks of colic. In those cases in which the stricture has been due to an operative injury to the duct the history is usually rather characteristic. In most cases, the patient will state that there was a profuse discharge of bile through the wound for a period of several weeks after the operation. As the discharge diminished jaundice and pain occurred, which was relieved only when the wound broke open again, resulting in a copious discharge of bile. This cycle may have been repeated several times. All of these occurrences are of course rather typical of an overlooked stone in the common duct. The picture, however, is even more confusing when the stricture has followed some years after an operation for cholecystectomy. It is certain that in rare instances a stricture, although it has followed an operation, has not been caused by an accidental injury to the ducts but has resulted from a continuation of inflammation already existing at the time of the operation or from an excessive production of scar tissue in the healing process. Usually the presence of a stricture can only be surmised unless there is definite knowledge that a duct was accidentally injured during an operation. Laparotomy is almost always necessary to establish

<sup>1</sup> Eliot, E., Jr.: *The Repair and Reconstruction of the Hepatic and Common Bile-ducts*, Surg., Gynec. and Obst., 1918, 26, 81.



the diagnosis. Occasionally a stone in the common duct has been recognized by roentgen-ray examination, especially if an opaque substance, such as lipiodol, has been injected into the biliary fistula. Cotte<sup>1</sup> has reported one such case. The prognosis in stricture is bad unless an operative repair can be made. See the chapter on Treatment for a more extensive discussion of this point.

### TUMORS OF THE DUCTS.

**Benign Tumors.**—The benign tumors of the bile-ducts are chiefly adenomas. Both cystic and solid forms are encountered. Most commonly they involve the intra-hepatic bile-ducts and therefore, when they are cystic, give rise to intra-hepatic cysts which may be very large. Shattuck,<sup>2</sup> for example, reported a supposed adenomatous cyst which contained as much as a gallon (about 4000 cc.) of fluid. Keen<sup>3</sup> also removed a large cystic adenoma. Besides the cystic adenomas there occur also multiple solid adenomas, which are most frequently found beneath the capsule of the liver as grayish-white nodules, which on cross-section somewhat resemble thyroid tissue because of their alveolar structure filled with secretion. The alveoli are lined with one or more layers of cubical or cylindrical epithelium. Apparently these tumors may undergo a transition into cystic adenoma and into carcinoma. Ewing gives an interesting discussion of them together with literature references. Fibromas, lipomas, etc., are of such rare occurrence that the correctness of the reports of the few cases in the literature is under suspicion, since in some cases no microscopic examination was made. The clinical features are not characteristic, and it is difficult to see how a clinical diagnosis could be made. In all of the cases reported, the diagnosis has been made only at operation or at postmortem examination.

**Malignant Tumors of the Ducts.**—Of the primary malignant tumors of the ducts, carcinoma is the only one which will be discussed because of the exceptional rarity of sarcoma. Moll,<sup>4</sup> however, has reported a case of a sarcoma of the ampulla of Vater composed of round and "oat-shaped" cells. Primary carcinoma arises both in the intra-hepatic and in the extra-hepatic ducts. Its most frequent site is at the junction of the cystic and common hepatic

<sup>1</sup> Cotte, G.: Sur l'exploration des voies biliaires au lipiodol en cas de fistule, *Médecine*, 1925, **7**, 42.

<sup>2</sup> Shattuck: *Boston Med. and Surg. Jour.*, vol. **143**.

<sup>3</sup> Keen, W. W.: Resection of the Liver, Especially for Hepatic Tumors, *Boston Med. and Surg. Jour.*, 1892, **126**, 405.

<sup>4</sup> Moll, H. H.: Sarcoma of the Ampulla of Vater, without Jaundice, Leading to Acute Pancreatitis, *Jour. Pathol. and Bacteriol.*, 1925, **28**, 528.

ducts, the place which it will be recalled is the most frequent site also of benign strictures of the ducts. Rolleston<sup>1</sup> states that in 80 cases the situation of the growth was as follows:

Common bile-duct:	
Lower end . . . . .	21
Middle part . . . . .	11
Junction of common bile-duct, cystic and common hepatic duct . . . . .	25
Common hepatic duct . . . . .	18
Right or left hepatic ducts . . . . .	3
In cystic duct . . . . .	1
In cystic duct and in lower end of bile-duct . . . . .	1

In contrast to the great frequency of gall stones with primary carcinoma of the gall bladder, calculi are comparatively infrequent in primary carcinoma of the ducts. In 40 cases collected by Devic and Gallavardin<sup>2</sup> gall stones were present in only 9 instances—6 times in the gall bladder and on 3 occasions in the bile-ducts; in only 1 case was the growth found to surround a calculus. In 62 of Rolleston's collected cases in which a definite statement as to the presence or absence of gall stones was made they were present in 23 and absent in 39. Rolleston also makes the significant statement, "the fact that gall stones are not so commonly met with in bile-duct carcinoma strongly supports the conclusion, formed on experimental grounds (Mignot), that calculi are not formed simply as a result of stagnation of bile due to obstruction set up by the growth. Stagnation is much more marked in bile-duct carcinoma than in similar disease of the gall bladder, and calculi are less common." Primary carcinoma of the ducts is slightly more frequent in males than in females, in about the proportion of 4 to 3; and it occurs most commonly after the age of fifty years. The infrequency of gall stones in association with primary carcinoma of the ducts lends probability to the idea which has been expressed by many that often this form of carcinoma probably originates in an adenoma of the duct. At any rate, this seems to be the most plausible explanation of the origin of that type which begins in the intra-hepatic ducts.

*Primary carcinoma of the intra-hepatic bile-ducts* is frequently multiple. These tumors are less frequently associated with cirrhosis than is the primary carcinoma which arises in the hepatic parenchymatous tissue. Ewing quotes Eggel as having found that 32 per cent of the primary carcinomas of the liver in his series were of ductal origin, but Pepere considered the incidence as only 14 per cent of all primary liver carcinomas. The liver is enlarged, often

<sup>1</sup> Rolleston, H.: *Diseases of the Liver, Gall Bladder and Bile-ducts*, 1905, W. B. Saunders Company, Philadelphia, p. 685.

<sup>2</sup> Cited by Rolleston: *Ibid.*, p. 684.

very greatly, deeply jaundiced and frequently shows evidence of marked biliary cirrhosis. The tumor affects a very large part of the liver, which is studded with numerous small firm nodules. It is usually impossible to determine any single primary focus. Many of the larger bile-ducts within the liver are greatly dilated. Microscopically these tumors are found to be essentially alveolar or adenocarcinomas. The epithelium resembles that which lines the bile-ducts and may be cylindrical or cuboidal. The stroma is well-marked and may contain elastic fibers. There is usually apparent a cicatricial contraction around the tumor nodules. The lumina of the alveoli are empty or are filled with bile or hyaline material. Metastases outside of the liver are not frequent but occasionally are found in the portal and mediastinal lymph nodes.

The clinical features will be discussed below.

*Carcinoma of the extra-hepatic ducts* appears generally in one of three forms: (1) Villous growths which may be single or multiple and fill the lumen of the duct; (2) nodular masses in the submucous and muscular coats of the duct which early encircle and constrict the duct; (3) extensive diffuse growths extending along the duct and converting it into a smooth rigid tube with occasional projections into the lumen of carcinomatous growths or of carcinomatous ulcers. Extensive metastasis, except in the liver, is not common. Usually extension occurs only along the duct. Sometimes the presence of multiple nodules within the liver makes a picture similar to that of primary carcinoma of the intra-hepatic ducts. If obstruction to the outflow of bile has occurred there is intense jaundice. If the tumor involves the hepatic duct above the junction with the cystic the gall bladder may be collapsed and comparatively empty. Wilkie<sup>1</sup> of Edinburgh, has made one such observation at operation. If, however, the tumor is situated below the cystic duct the gall bladder will generally be distended with bile. If it is located at the junction of the cystic and common hepatic ducts the gall bladder may show a hydrops but will contain no bile if the obstruction is complete. Microscopically, carcinomas of the large hepatic ducts closely resemble carcinomas of the gall bladder except that there is usually a greater fibrosis in the ductal tumors. The epithelial elements in some cases are so small in comparison with the large amount of fibrous tissue that, unless careful microscopic examination is made, it would be easy to make the error of diagnosing a benign stricture instead of a carcinoma. In one case in our own experience

<sup>1</sup> Wilkie, D. P.: Personal communication.

which came to postmortem examination a diagnosis of benign stricture was first made by the pathologists, and the true malignant nature of the condition was recognized only after making a large number of sections. In that case the tumor was in the lower portion of the common duct. Generally these tumors are of an adenocarcinomatous type with cylindrical cells which produce mucus. The clinical features will be discussed below.

*Carcinoma of the region of the ampulla of Vater* is comparatively rare. Rolleston stated in 1925 that he was able to find only 22 cases which he considered as genuine examples. Cohen and Colp,<sup>1</sup> however, have recently collected reports of 59 cases in which operations were performed. Within an area with a radius of not more than  $\frac{1}{4}$  inch carcinoma may arise in any one of the following structures: (1) The ampulla of Vater; (2) the end of the common bile-duct; (3) the end of the duct of Wirsung; (4) the glandular tissue of the head of the pancreas; (5) the duodenal mucous membrane covering the biliary papilla. Of the 22 cases, 15 were males with an average age of fifty-seven years, and 7 females with an average age of fifty years. The extreme ages were thirty-four and eighty-one years. In only 3 cases were gall stones present. With the exception of the duct of Wirsung, which is said to consist of spheroidal cells, like the carcinoma arising in the head of the pancreas, all the other carcinomas in this region are columnar-celled. One of the striking features of carcinoma in this region is the fact that usually it is very small. Some of those which have caused death either from obstruction or from hemorrhage have been only a centimeter or less in diameter. It is obvious that because of the anatomical relations a growth in the region of the ampulla may easily at an early stage produce obstruction of the common bile-duct or of the duct of Wirsung. If the former has been obstructed jaundice will occur and the same effects on the liver and gall bladder will take place as those produced by a carcinoma of the lower portion of the common bile-duct. In accordance with Courvoisier's law the gall bladder in such cases will usually be distended with bile. Suppurative cholangitis may also occur, but this complication seems to be most frequent in association with carcinoma of the duodenal surface of the biliary papilla. If the duct of Wirsung is obstructed an interstitial pancreatitis without glycosuria generally results. Metastases are not common, probably because life does not con-

<sup>1</sup> Cohen, I. and Colp, R.: Cancer of the Periapillary Region of the Duodenum, Surg., Gynec. and Obst., 1927, 45, 332.



tinue long enough as a rule on account of the early obstruction of the common bile-duct and the development of cholemia.

*The clinical features of carcinoma of the bile-ducts* are sufficiently similar for all the types of tumor to permit a discussion of all of them together. The *onset* is insidious, and generally the first sign is jaundice, although this may be preceded by vague upper abdominal distress. The most characteristic clinical features are the progressive increase of the jaundice without intermissions and without attacks of pain. With the increasing development of biliary obstruction other subsidiary signs occur, such as itching of the skin, a tendency to hemorrhage, mental confusion, etc. The liver is generally enlarged, and in about one-half the cases a distended gall bladder can be palpated. The smooth surface of the latter tends to distinguish it from a carcinoma of the gall bladder. Ascites is not a conspicuous clinical feature, but according to Devic and Gallavardin some ascites is found in one-half of the cases which are examined postmortem. In their 55 collected cases the spleen was palpable in 8. The urine is bile-stained, less than normal in quantity, and frequently contains casts. If suppurative cholangitis supervenes, chills and fever are likely to occur. After the jaundice has become extreme the clinical course is seldom longer than six months. The *diagnosis* of malignant obstruction of the bile-ducts is almost certainly correct if the patient is past fifty years of age and has shown a painless progressive jaundice with loss of weight, and with a palpable distended gall bladder. The obstruction, however, is not necessarily due to a carcinoma which has originated in the bile-ducts. Primary carcinomas of the head of the pancreas, for example, often cause obstruction of the common bile-duct by pressure. In obstruction of the common duct from stone, attacks of biliary colic and intermissions in the degree of jaundice are the rule. It is not usually possible, however, to diagnose by clinical means the location of the obstructing carcinoma. A distended gall bladder will, of course, indicate that the obstruction is situated below the junction of the cystic with the common hepatic duct. Rolleston states that the following points are in favor of the carcinoma's being at the ampulla of Vater: Intermissions in the jaundice (but these are usually slight), fever from infection of the bile-ducts and attacks of diarrhea. The syndrome of so-called "catarrhal icterus" usually begins with more or less severe gastro-intestinal symptoms, such as nausea, vomiting, diarrhea, etc., while the onset of primary carcinoma of the ducts is almost always insidious without such symptoms. We have had only one experience with cholecystography in cases of

primary carcinoma of the ducts, that one a primary tumor of the cystic duct. In this case no shadow of the gall bladder was revealed, a finding which would be expected because of the obstruction of the duct.

### BILIARY FISTULÆ.

Biliary fistulæ arise spontaneously and as a result of injury. The spontaneous fistulæ are probably always the result of inflammatory or malignant ulceration which establishes an abnormal passage between the biliary tract and some other organ or which leads to an outpouring of bile through an external opening in the abdominal wall.

**External Fistulæ.**—External fistulæ are of course the most commonly recognized form. Out of 384 cases of spontaneous biliary fistulæ of all kinds, but associated with gall stones, which were collected by Naunyn,<sup>1</sup> 184 were external from the gall bladder. When of spontaneous origin they are usually located near the umbilicus or in the right upper quadrant, but occasionally they occur in the right lower quadrant and even in the thigh. Usually they lead by a more or less tortuous passage from the gall bladder rather than from the ducts. They are usually secondary to a suppuration within or near the gall bladder and in the majority of instances they are associated with the presence of calculi. When, however, external fistulæ follow operations on the biliary tract they are then of course situated in the operative scar. Postoperative external biliary fistulæ may signify a number of conditions. In former times when the operation of drainage of the gall bladder was more commonly performed than now, these fistulæ were much more frequent. They were especially prone to follow that type of cholecystostomy in which the gall bladder was sutured to the abdominal wall. If, as was frequently done, prolonged drainage was encouraged by allowing the tube to remain for many weeks there was abundant opportunity for epithelialization of the fistulous tract to occur so that a permanent fistula would result. But even with the more modern methods of surgical drainage biliary fistulæ from the gall bladder still occur occasionally. In the majority of instances such fistulæ signify that an obstruction of the common duct is present, and usually this is due to a stone that has been overlooked and allowed to remain in the duct. In other cases it is due to stricture of the duct either from scar tissue or malignant growth, and in still others the explanation is difficult to determine since at a later operation no obstruction of the duct may be

<sup>1</sup> Naunyn: On Cholelithiasis, p. 143, English edition.

found. The clinical picture of an external postoperative biliary fistula due to a stone in the common duct is rather characteristic, and in the majority of cases it serves to establish the diagnosis. In such cases the fistula will often heal temporarily, to be followed by jaundice and discomfort or even actual attacks of biliary colic. When the fistula breaks open again with a copious discharge of bile the jaundice and the discomfort will disappear. This cycle may be repeated frequently. If, however, the fistula is associated with malignant obstruction of the duct there is less tendency for it to heal even temporarily, probably because since the obstruction is complete and permanent the bile is continuously forced out of the fistulous opening. Postoperative external biliary fistulæ following cholecystectomy usually signify either an overlooked stone in the duct or an accidental injury of the common or of an hepatic duct. If a stricture occurs from the later formation of fibrous tissue the cycle may take place of temporary closure to be followed by more intense jaundice and pain, such as has been described above, as characteristic of an overlooked stone. In the section on benign strictures of the ducts the clinical features have been described more extensively. A roentgen-ray film taken after the injection of lipiodol into the fistulous tract, as suggested by Cotte,<sup>1</sup> in at least one case has demonstrated a stone in the common duct. This method may prove to be of great value in such cases.

**Mucous Fistula.**—Closely related to the external biliary fistulæ is the mucous fistula, which occurs sometimes after the operation of cholecystostomy. In this condition there is a discharge of thin, stringy, almost transparent mucus without bile. This discharge represents the more or less normal secretion of the mucosa of the gall bladder; and the presence of an external mucous fistula after cholecystostomy signifies an obstruction of the cystic duct, which is almost always due to a stone impacted in the duct. Bile cannot enter the gall bladder because of the obstruction in the cystic duct and therefore it does not appear in the discharge from the fistula.

**Duodenal Fistula.**—Another fairly common variety of biliary fistula is that which leads into the gastro-intestinal canal. Several kinds exist, of which the most frequent is the duodenal fistula. In Naunyn's<sup>2</sup> 384 cases the duodenum was involved in 108. Again, of these 108 cases, in 98 the communication was between the fundus of the gall bladder and the first part of the duodenum. In 153

<sup>1</sup> Cotte, G.: Sur l'exploration des voies biliaires au lipiodol en cas de fistule, *Médecine*, 1925, 7, 42.

<sup>2</sup> Naunyn: *Ibid*,

cases of internal biliary fistula which were operated upon at the Mayo Clinic and reported by Judd and Burden<sup>1</sup> there were 117 of fistula with the duodenum and 4 others of combined openings into the duodenum and colon. Duodenal fistula is most frequently due to the ulceration of a stone through the wall of the gall bladder. Occasionally there has been severe hemorrhage resulting from the ulceration which has been thought to be due to an ordinary peptic ulcer of the duodenum or of the stomach. In some cases symptoms of pyloric obstruction have occurred because of the obstruction of the duodenum by scar tissue after the formation of the fistula. The amount of fibrous tissue may be very great and may be suggestive of malignancy at operation. There may also be actual ulceration of the mucous membrane of the duodenum with vomiting and other symptoms, even when there is no obstruction. Finally, because of inflammation and abscess formation there may be multiple fistulous openings not only into the duodenum but into other organs as well. *Fistulæ between the common duct and duodenum* also occur. This type occurred in only 15 of Naunyn's 108 cases but Naunyn thinks that they are probably much more common than the reported cases would indicate.

**Gastric Fistulæ.**—Biliary gastric fistulæ are much less frequent than the duodenal variety. There were only 12 of these in Naunyn's 384 cases and 6 in Judd's and Burden's 153 cases. There are no particularly characteristic symptoms of this type of fistula. Occasionally, however, gall stones have been vomited, and in such cases the inference is strongly suggestive that the fistula is gastric, although it is possible that also in a high duodenal fistula there might be vomiting of calculi.

**Cholecystocolic Fistulæ.**—Cholecystocolic fistulæ occurred in 49 of Naunyn's 384 cases and in 26 of Judd's and Burden's 153 cases. These fistulæ are likely to produce a fairly characteristic clinical picture. Diarrhea and emaciation are commonly present because since the bile is poured out into the large intestine it serves no purpose in the digestion of fat. The stools therefore are sometimes fatty and clay-colored in their interior although their exterior may be bile-stained. Large amounts of bile of unchanged color may be noted in the stools. *Fistulæ into the small intestine* are much less common. Naunyn, however, refers to 2 cases.

A clinical diagnosis of a gastro-intestinal biliary fistula can rarely be made. All the patients, however, have very pronounced signs

<sup>1</sup> Judd, E. S. and Burden, V. G.: Internal Biliary Fistula, *Ann. Surg.*, 1925, **81**, 305.



and symptoms of severe disease of the biliary tract. Roentgen-ray examination with the barium meal sometimes reveals a gastro-intestinal biliary fistula. It is possible also that in some instances cholecystography will be of assistance in making a diagnosis, but up to the present time we have had no experience with it in this connection. At operation the finding of very dense adhesions between the gall bladder and some part of the gastro-intestinal canal should always arouse suspicion of a fistula. Judd and Burden also emphasize the great diagnostic importance of foul bile or of frothy thick mucus in the gall bladder.

In all types of gastro-intestinal biliary fistulæ serious effects on the bile tract and the liver are likely to occur. In some instances, as in the duodenal and gastric varieties, the entrance of the digestive juice into the gall bladder is likely to produce a serious inflammation, and in the case of the colonic fistulæ the entrance of masses of fecal material is likely to have the same effect. In any case the liver may contain multiple abscesses as the result of an ascending inflammation. In exceptional instances large gall stones which have found their way into the intestine from the gall bladder by ulceration have produced obstruction of the intestinal lumen. Associated with the inflammation which produces the fistula there is sometimes so much inflammation of the bowel that extensive necrosis occurs.

**Broncho-biliary Fistulæ.**—The broncho-biliary fistulæ constitute another type less commonly observed than gastro-intestinal fistulæ. In 1897 J. E. Graham<sup>1</sup> was able to collect 34 cases of this condition including 2 of his own. A few of these cases were associated with hydatid cysts of the liver but the majority have been associated with gall stones. In one of Graham's cases the fistula followed a kick by a horse in the region of the liver, and the patient began to cough up bile in about two and a half weeks after the injury. The essential pathogenesis of the condition is the formation of an abscess which ulcerates through the diaphragm into the lung. Most of these abscesses lead from the convex surface of the right lobe of the liver. The amount of bile expectorated has been as much as 700 cc. per day in some cases. Dulness has usually been found present over the right thorax, extending in some cases as far back as the mid-axillary line and forward and inward to the margin of the sternum and upward as far as the third intercostal space. Occasionally dulness has been found posteriorly. We have found no cases reported in which an examination by roentgen-ray has been made. Cough is

<sup>1</sup> Graham, J. E.: Two Cases of Broncho-biliary Fistula, Trans. Assn. Am. Phys., 1897, p. 247.

usually a very distressing symptom. In one of Graham's cases the patient's symptoms completely disappeared spontaneously and he remained entirely well for ten years, after which the symptoms returned. Usually, however, if the symptoms disappear there is no recurrence. Oliani<sup>1</sup> in 1923 published a summary of 63 cases, including many of echinococcus origin.<sup>2</sup>

Other types of fistulæ which are rare are *cholecysto-renal*, *cholecysto-vaginal*, those between the *gall bladder* and *urinary bladder*, between the *gall bladder* and *portal vein*, and in a single reported instance one between the *pericardium* and the *biliary tract*.

<sup>1</sup> Oliani: Ann. Ital. di Chir., Napoli, 1923, **2**, 1075, 1288.

<sup>2</sup> In an article which has just appeared Morton and Phillips have published an extensive review of all of the cases in the literature in which there was a broncho-biliary fistula not due to an amebic abscess or to an infection with the echinococcus. (Morton, J. J., and Phillips, E. W., Bronchobiliary Fistula: Review of the Recorded Cases Other than Those Due to Echinococcus and Amebic Abscess, Arch. Surg., 1928, **16**, 697.)

## CHAPTER VII.

### THE RADIOLOGY OF THE BILIARY TRACT.

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#### SECTION I.

##### HISTORICAL SKETCH.

**Introductory.**—For complete understanding of the application of radiological procedures to the study of the biliary tract, it is necessary to review events from the first efforts in this direction to conditions and usage as found at present. Radiological applications in this field fall into three natural epochs, which are clearly defined, except chronologically. The first of these periods begins almost with the discovery of the roentgen-rays, and extends to that time when radiography had become an important adjunct in the examination of the gastro-intestinal tract with the fluoroscope and opaque meal. It ends about the year 1910. It is characterized by investigation of the composition, structure, and density of gall stones as revealed by roentgen-rays, and attempts at their demonstration *in situ*. It is notable for early enthusiasm for the roentgen method of study of cholelithiasis, which gradually waned until most workers abandoned the roentgen-ray search for biliary calculi.

The second period opens as indicated, and terminates with the discovery of cholecystography, in 1923. In its initial stage there was a revival of the effort to demonstrate gall stones, this resulting from the employment of radiography in examining the alimentary tract. The indirect or subsidiary signs of the diseased gall bladder and its effect on other abdominal structures were discovered and developed. The latter will be elaborated on later. It represents an important phase of biliary-tract radiography because in some degree due weight is given for the first time to the pathological gall bladder as such, and its possible results; that is to say, attention was directed toward infection, the formation of gall-bladder adhesions and their effect on adjacent structures, stomach, duodenum, and colon.

The story of the development of the radiology of the biliary

tract during the first two periods is in reality the story of the development of radiography. Necessarily this meant that efforts in this direction improved in ratio to the improvement in generating plants (static machine, induction coil, transformer), X-ray tubes, intensifying screens, films, and the perfection of the Potter-Bucky diaphragm. Furthermore, as proficiency with the opaque meal in the alimentary tract grew, the shortcomings of the fluoroscopic method in this procedure led more and more to resort to radiography in the more difficult cases. This naturally attracted attention to the possibilities of radiography in studying the biliary tract. The termination of the second period of gall-tract radiology is marked by general dissatisfaction with the uncertain results even from the best methods, and a search for means to improve upon them. Among these may be mentioned the recommendation of gastric and colonic inflation, later the use of pneumoperitoneum, and a method mentioned only to be condemned, of direct puncture of the gall bladder through the abdominal wall and injection of a dense contrast medium, practised by Burekhardt and Müller.<sup>1</sup> The climax of all of these endeavors at improvement over usual roentgen-ray procedures was the discovery of cholecystography, in 1923.<sup>2</sup>

**The Origin of Gall-tract Radiography.**—Reverting to the earliest period, one of the early medical applications of Roentgen's discovery was the study of the abdominal cavity and its contents. These are of such uniform density that it was at once apparent that this means was useless for discovering pathological conditions, except those that had some degree of calcification as a feature. It is true that in relation to the biliary tract a small amount of information in regard to the liver could be gleaned from this method because of the fact that the upper surface of the right lobe of the liver is outlined by the aerated right lung and the diaphragm. It followed that those engaged in the medical application of roentgen-rays turned their attention toward the search for intra-abdominal calcification, and it naturally occurred that their efforts were directed to the detection of gall stones.

The first roentgen-ray investigation of gall stones was done in 1897, by Gilbert, Fournier and Oudin,<sup>3</sup> who studied them outside

<sup>1</sup> Burekhardt, H. and Müller, W.: Versuche über die Punktion der Gallenblase und ihre Röntgendarstellung, *Deutsch. Ztschr. f. Chir.*, Leipzig, 1921, **162**, No. 3-4, 168.

<sup>2</sup> Graham, E. A. and Cole, W. H.: Roentgenologic Examination of Gall Bladder; Preliminary Report of a New Method Utilizing Intravenous Injection of Tetra-bromphenolphthalein, *Jour. Am. Med. Assn.*, 1924, **82**, 613.

<sup>3</sup> Gilbert, Fournier and Oudin: Photographie des calculs biliares par les rayon-X, *Compt. Rend Soc. de biol.*, Paris, 1897, **4**, 506.



the body and expressed the opinion that this means was useless until such time as great improvement had been developed. Matthias and Fett<sup>1</sup> relate that in 1896 Chappuis and Chauvel claimed it was undoubtedly possible to demonstrate stones in either the kidney or gall bladder, provided they were not overlying the ribs. (The original article could not be found.) The first writers mentioned above reached their conclusions on the ground that most stones are composed of cholesterol and are therefore very permeable to the roentgen-ray. It should be mentioned at this point that a urinary calculus was first found by McIntyre,<sup>2</sup> of Glasgow, in 1896, and that Williams,<sup>3</sup> writing in 1903, reported 35 cases of urinary calculi surgically confirmed. Undoubtedly, success in this direction had much to do with stimulating roentgen-ray search for biliary calculi. The dissimilarity in composition, chiefly in the direction of the greater density of urinary over biliary calculi, rendered the procedure far more valuable in the case of the former than of the latter.

The first demonstration of a gall stone in a living subject is commonly ascribed to Beck,<sup>4</sup> of New York, in 1900. He quoted several German authors to the effect that gall stones could not be detected by roentgen-rays. However, he had been endeavoring to accomplish this since February 1896. From that date he had examined 28 cases, making 97 plates. Nine of the 28 cases were found at operation to have stones. He was finally successful in discovering gall stones in 2 cases. He claimed that this detection by the roentgen-ray depended on the amount of calcium which they contained, and that pure cholesterol stones could not be found by this means.

Unquestionably, Buxbaum,<sup>5</sup> of Karlsbad, preceded Beck by two years in the publication of successful radiography of gall stones. Out of 30 attempts on living subjects he demonstrated them in 4 cases. He concluded that the method promised much as it improved and knowledge increased. Having attempted, with a fluoroscope, to visualize a gall stone held between the fingers, he made the significant observation that it would never discover a calculus in the body, a statement which, with rare exceptions, still holds good.

<sup>1</sup> Matthias, F., and Fett, E.: Die Aussichten der Röntgenographie des Gallenkonkrements, Fortschr. auf. dem Gebiete der Röntgenstrahlen, 1906-1907, **10**, 199.

<sup>2</sup> McIntyre, John: Photography of Renal Calculus, Lancet, July 11, 1896.

<sup>3</sup> Williams, Francis H.: The Roentgen-rays in Medicine and Surgery, 3d ed., 1903, Macmillan Company, p. 623 *et seq.*

<sup>4</sup> Beck, Carl: On the Detection of Calculi in the Liver and Gall Bladder, New York Med. Jour., 1900, **71**, 73.

<sup>5</sup> Buxbaum, A.: Ueber die Photographie von Gallenstein *in vivo*, Wien. med. Presse, 1898, **39**, 534.

Numerous workers studied gall stones outside the body, and in various media, to determine whether or not their demonstration in the living subject was possible. Among these are Gilbert, Fournier and Oudin,<sup>1</sup> already mentioned, in France, Luis y Yague and Gaztelu<sup>2</sup> in Spain, and Fornario,<sup>3</sup> in Italy. The consensus of opinion of these workers was that, depending upon the composition of the stone (that is, whether or not it contained sufficient calcium), with improvement in methods and apparatus, the roentgen-ray would in a certain proportion of cases be useful in searching for gall stones in the human. Among the early gall stone demonstrations, aside from the examples of Buxbaum<sup>4</sup> and Beck,<sup>5</sup> were those of Mauclaire and Infroit,<sup>6</sup> in France (1903), and Holland,<sup>7</sup> in England (1905). Matthias and Fett,<sup>8</sup> publishing in 1906 to 1907, were of the opinion that the finding of gall stones had been so infrequent that in 1905 there was only one view of the procedure, and that was unfavorable. However, the question whether, with the elimination of the difficulties of poor technique, visualization was possible, must be answered in the affirmative. They reported several cases themselves, and pointed out that the obstacle to visualization was not due to the permeability of the stones, but rather to lack of contrast in density with the surrounding medium.

It is worth noting here that the earliest cases of visualization of gall stones required several roentgen-ray exposures of from three to ten minutes' duration. In spite of the small current capacity of the roentgen-ray tube of those days, one ponders the lack of reported burns.

Gottschalk<sup>9</sup> reported a gall stone found by the roentgen-ray, and stated that such a finding was so rare that it would be well to report all successful examples of this. He was led to this conclusion

<sup>1</sup> Gilbert, Fournier et Oudin: Photographie des calculs biliaires par les rayon-X Compt. rend. Soc. de biol., Paris, 1897, **4**, 506.

<sup>2</sup> Luis y Yagüe, R. and Gaztelu, F.: Valor diagnostico de la radiografia en la litiasis biliar vesicular, Siglo méd., Madrid, 1903, **50**, 553.

<sup>3</sup> Fornario: Dell'uso del raggi X nella diagnosi dei calcoli delle vie biliari, Gazz. internaz. di med., Naples, 1903, **6**, 193.

<sup>4</sup> Buxbaum, A.: Ueber die Photographie von Gallenstein *in vivo*, Wien. med. Presse, 1898, **39**, 534.

<sup>5</sup> Beck, Carl: On the Detection of Calculi in the Liver and Gall Bladder, New York Med. Jour., January 20, 1900, vol. **71**.

<sup>6</sup> Mauclaire and Infroit: Diagnostique des calculs biliaires par la radiographie preliminaire, Compt. rend. Acad. d. sci., Paris, 1903, **137**, 482.

<sup>7</sup> Holland, C. Thurston: On Gall Stones, Liverpool Med. and Chir. Jour., 1914, **34**, 308.

<sup>8</sup> Matthias, F., and Fett, E.: Die Aussichten der Röntgenographie des Gallenkonkrements, Fortschr. auf dem Gebiete der Röntgenstrahlen, 1906-1907, **10**, 199.

<sup>9</sup> Gottschalk, Edward: Ueber einen Fall röntgenographisch nachgewiesener Gallensteine, Fortschr. auf dem Gebiete der Röntgenstrahlen 1909-1910, **14**, 12.

because of an incorrect diagnosis between kidney and gall stone, with operation for the former when the latter was present. Arcelin<sup>1</sup> reported two examples of biliary calculi with identical confusion of diagnosis as in the preceding case, followed by an unnecessary operation. He stated that it was generally accepted in France that the roentgen-ray will not discover biliary calculi, and that so few surgeons have had an opportunity of seeing radiographs of them that institutions should have all suspected cases regularly roentgen-rayed. Witte,<sup>2</sup> writing in 1914, arrives at the same conclusion, and for the same reasons. Occasionally a calcified gall bladder is seen, a finding which is definite evidence of chronic cholecystitis. (Figs. 86 and 87.)

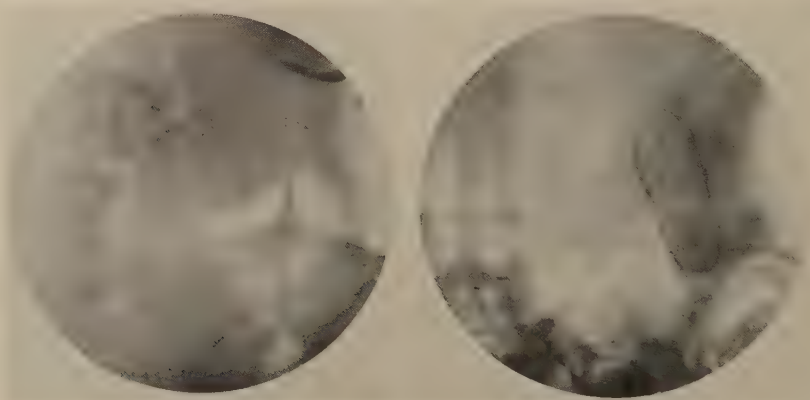


FIG. 86

FIG. 87

FIGS. 86 and 87.—Two cases of calcified gall bladder. Seen in plain roentgen-ray films without cholecystography.

**The Discovery of the Indirect Signs of the Pathological Gall Bladder.**—Turning away from biliary calculi to the indirect signs of gall-bladder disease, Schürmayer<sup>3</sup> studied the matter of adhesions and their effects in the right upper abdominal quadrant when observed by means of the opaque meal. He found that in gall-stone disease pericholecystitis occurs much more frequently than is generally supposed. Among other things, he stated that in the

<sup>1</sup> Arcelin, M.: *Les calculs biliaires causes d'erreur en radiographie rénale*, Lyon méd., 1913, 1, 1129.

<sup>2</sup> Witte, J.: *Ein Fall von besonders deutlichen Gallensteinnachweis durch Röntgenlicht*, Fortschr. auf dem Gebiete der Röntgenstrahlen, 1914-1915, 22, 217.

<sup>3</sup> Schürmayer, C. B.: *Pathologische Fixation bzw. Lagveränderung bei Abdominalorganen und die röntgenologische Diagnosestellung*, Fortschr. auf dem Gebiete der Röntgenstrahlen, 1910, 15, 308.

swelling of the liver often characteristic of cholelithiasis, the gall bladder is brought nearer to the stomach and the pericholecystitis may extend to the latter; when the swelling of the liver subsides, either spontaneously or through treatment, the pylorus is drawn into the right side of the abdomen. He differentiated the origin of pericholecystic adhesions, holding that a second such group are to be traced to ulcer, either duodenal or gastric. In addition to adhesions between gall bladder and stomach or duodenum, he called attention to those involving the colon, which sometimes give rise to a second or pseudo hepatic flexure. This author is quoted by Pfahler,<sup>1</sup> who wrote that when adhesions in the gall-bladder region have taken place and can be verified, we have in the roentgen-rays a means of diagnosis of biliary-tract disease which is distinctly more valuable than the direct examination for gall stones. He also pointed out that the indefinite symptoms found in such cases might be explained by the interaction of the organs concerned through the attaching adhesions.

From the last-named date, there was notable development of roentgen-ray examination of the right upper quadrant and the biliary tract by Case,<sup>2</sup> Pfahler,<sup>3</sup> L. G. Cole,<sup>4</sup> George<sup>5</sup> and L. G. Cole, in this country, McLeod,<sup>6</sup> in Shanghai, and Knox,<sup>7</sup> in England.

But it was probably the work of L. G. Cole with serial radiography on diseases of the stomach and the duodenal cap, that gave the greatest impetus to the radiographic study of the gall bladder. George<sup>5</sup> states that it was this that led him into a systematic roentgen-ray study of the gall bladder and its ducts.

L. G. Cole,<sup>9</sup> writing in 1914, is more emphatic than Pfahler in

<sup>1</sup> Pfahler, George E.: Gastric and Duodenal Adhesions in the Gall Bladder Region and their Diagnosis by the Roentgen-rays, *Jour. Am. Med. Assn.*, 1911, **56**, 1777.

<sup>2</sup> Case, James T.: Roentgenography of the Liver and Biliary Passages, with Special Reference to Gall Stones, *Jour. Am. Med. Assn.*, vol. **61**, p. 920; Some Statistics on the Negative and Positive Roentgen Diagnosis of Gall Stones, *Am. Jour. Roentgenol.*, 1916, **3**, 246.

<sup>3</sup> Pfahler, George E.: Roentgen-rays in the Diagnosis of Gall Stones and Cholecystitis, *Jour. Am. Med. Assn.*, vol. **62**, No. 17, p. 1304.

<sup>4</sup> Cole, L. G.: The Detection of Pure Cholesterin Gall Stones, *Am. Jour. Roentgenol.*, vol. **2**, No. 4, p. 640; The Roentgenographic Diagnosis of Gall Stones and Cholecystitis, *Surg., Gynec. and Obst.*, vol. **18**, p. 218.

<sup>5</sup> George, A. W. and Cole, L. G.: The Roentgen Diagnosis of Gall Stones by Improved Methods, *Boston Med. and Surg. Jour.*, vol. **172**, p. 326.

<sup>6</sup> McLeod, N.: Radiography of the Gall Bladder, *Arch. Radiol. and Electrother.*, 1920-1921, **25**, 141, 181.

<sup>7</sup> Knox, Robert: Roentgen Examination of Liver, Gall Bladder and Bile-ducts, *Arch. Radiol. and Electrother.*, July, August, September and October, 1919, vol. **24**.

<sup>8</sup> George, A. W. and Leonard, R. D.: The Pathological Gall Bladder, Paul B. Hoeber, Inc., New York, 1922.

<sup>9</sup> Cole, L. G.: Roentgenographic Diagnosis of Gall Stones and Cholecystitis, *Surg., Gynec. and Obst.*, 1914, **18**, 218.



regard to pericholecystitis and its significance, believing that it is a stronger indication for surgical procedure than a disclosed calculus, for the reason that the adhesions indicated infection, requiring surgical intervention, while a non-infected gall bladder with stone may cause no symptoms. He believed also that there was a sufficiently large number of gall stones discoverable with the roentgen-ray to justify search for them.

**Other Presumptive Signs of the Pathological Gall Bladder.**—So far we have dealt chiefly with the most reliable signs of gall-bladder disease, that is, the presence of stones, and the secondary signs of fixation or dislocation of the structures of the right upper quadrant. George and Leonard<sup>1</sup> called attention to another indirect sign,

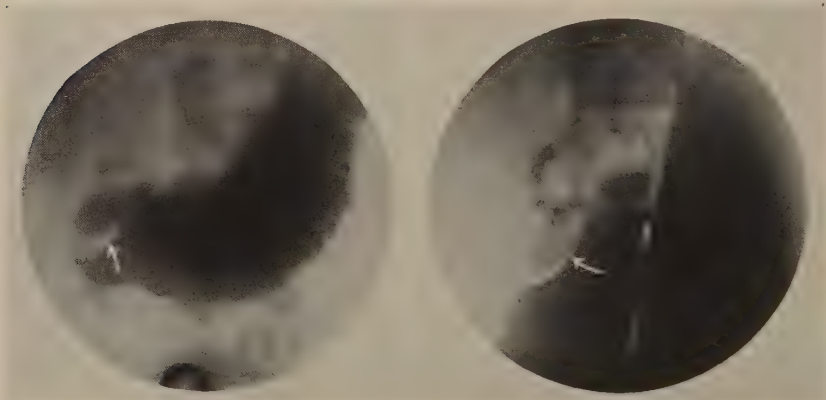


FIG. 88

FIG. 89

FIGS. 88 and 89.—Arrows indicate impressions on the antrum of the stomach, presumably from a distended gall bladder.

the impression made by a distended, tense gall bladder on adjacent hollow structures filled with opaque material, the duodenal cap, the antrum of the stomach, and occasionally the colon, producing curvilinear extraneous filling defects. (Figs. 88 and 89.) Their explanation of them was that the tension in a diseased gall bladder is greater than that in the other structures; therefore it indents them. They also added another direct sign of cholecystitis, namely, the finding of the gall-bladder shadow on the roentgen-ray film, their working hypothesis being that if this occurs the organ is pathological, and conversely, that a normal gall bladder is never visualized.

<sup>1</sup> George, A. W. and Leonard, R. D.: Roentgen Diagnosis of Pathological Gall Bladders, *Am. Jour. Roentgenol.*, 1917, 4, 321.

These two theories of George and Leonard derived from the study of gall-bladder disease have given rise to so much difference of opinion that in this country there have been practically two schools of thought on the subject. It is noteworthy that in the same article they state that surgeons cannot tell by palpation and inspection at operation whether or not a gall bladder is diseased, in which view they have support, which will be given later.

Probably because of war conditions, from the year 1914 to the discovery of cholecystography publications dealing with the roentgen-ray study of the gall-bladder region were chiefly by Americans, and their opinions and work were quite generally accepted. The discovery of the Potter-Bucky diaphragm, the introduction of the double-coated film with double intensifying screen, and to a less extent the application of pneumoperitoneum, added greatly to the satisfactory results obtained from the roentgen-ray examination in disease of the biliary system.

**The Differentiation of Dense Bodies Found in the Right Upper Quadrant.**—Before leaving this subject, and because it will have a considerable bearing on cholecystography, the matter of differentiation of dense bodies in the right upper quadrant discovered in the course of its roentgen-ray examination, may be discussed. The differential points between renal and biliary calculi appear to us to be best classified by L. G. Cole,<sup>1</sup> and are as follows:

1. Renal calculi are usually very dense; biliary calculi may be either soft or dense.

2. Renal calculi are usually single; biliary calculi are usually multiple.

3. Renal calculi are usually of the same density throughout; biliary calculi usually have a variable density, many times showing only a ring-like shadow or a dense nucleus.

4. Multiple renal calculi usually have an irregular shape, the size and shape conforming to the pelvis or calices; multiple biliary calculi, where they fill the gall bladder, usually conform to the pear-shaped gall bladder.

5. Multiple renal calculi usually vary in size and shape; multiple biliary calculi usually have relatively the same size and shape.

6. In renal calculi the surfaces are usually rounded; in biliary calculi the surfaces are usually faceted.

7. Renal calculi frequently are branching with irregularities

<sup>1</sup> Cole, L. G.: *Diagnosis between Right-renal and Gall-bladder Lithiasis*, *Interstate Med. Jour.*, 1917, **24**, 946.

conforming to the pelvis and calices; biliary calculi are never branching, but do occasionally have flat surfaces.

8. Renal calculi seldom change their position between examinations; biliary calculi frequently change their position between examinations.

The necessity for such differentiation will depend to a great extent on the urological facilities at hand. Pyelography will in many instances decide which type of calculus is present. However, as pointed out by McLeod,<sup>1</sup> this will not always be possible, as a calcified body may lie in line with the image of the kidney pelvis and be effaced in the same fashion as if it were within the kidney pelvis. In such event resort may be had to shifting of the tube,



FIG. 90



FIG. 91

Figs. 90 and 91.—Examples of "ring" gall stones, indicated by arrows.

with two exposures, films made in both the dorsal and ventral postures, and their comparison as to size, lateral radiography with the right side to the film, and the stereoscopic method with either the dorsal or ventral decubitus, the last manœuvre recommended, among others, by Manges,<sup>2</sup> L. G. Cole<sup>3</sup> and Knox.<sup>4</sup> Cholecystography in certain of these difficult cases will be most useful, and its application to them will be discussed later. Other shadows found

<sup>1</sup> McLeod, N.: Radiography of the Gall Bladder, *Arch. Radiol. and Electrother.*, 1920-1921, 25, 141, 181.

<sup>2</sup> Manges, W. F.: *Non-surgical Drainage of the Gall Tract*, Lyon, Lea & Febiger, Philadelphia, 1923, chap. vx, p. 377.

<sup>3</sup> Cole, L. G.: Diagnosis between Right-renal and Gall-bladder Lithiasis, *Interstate Med. Jour.*, 1917, 24, 946.

<sup>4</sup> Knox, Robert: *Radiography in the Examination of the Liver, Gall Bladder and Bile-ducts*, C. V. Mosby Company, St. Louis, 1921.

in the right upper quadrant may be produced by calcification of any nature, either intra-abdominal (Figs. 90, 91, 92, 93, 94, 95 and 96) or parietal, the most frequent being calcified costal cartilages and lymph nodes, which, however, generally differ from either biliary or renal calculi in the density, uniformity and distribution of the contained calcium (Figs. 97 and 98). Tumors of the skin (*e. g.*, mole) can produce an image on a radiograph strikingly similar to either biliary or renal calculus, as has been shown by Dodd and Case.<sup>1</sup> Rarely, a foreign body in the intestines may lead to error. Carman<sup>2</sup> calls attention to the possibility of like difficulty arising from the presence of a desmoid tumor of the anterior abdominal wall when the patient is rayed when in the ventral decubitus. In

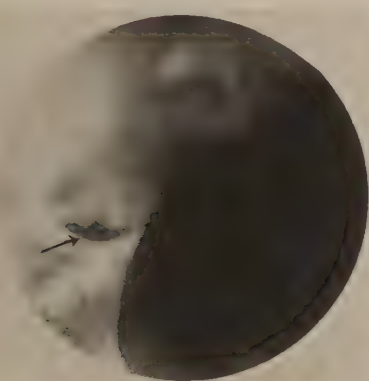


FIG. 92

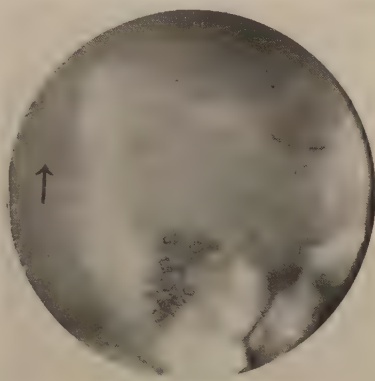


FIG. 93

FIGS. 92 and 93.—Multiple gall stones. Fig. 92: Patient erect. Fig. 93: Patient prone. Arrow indicates a small stone, presumably in the common duct.

spite of the manoeuvres and resources at hand to distinguish between the images which may appear in radiographs of the right upper abdominal quadrant, the differential diagnosis of lesions of that region certainly appears to be a difficult one in view of the statement of Nichols<sup>3</sup> that 30 per cent of the renal cases which he was called on to examine had had an antecedent right abdominal operation. Approximately the same percentage has been mentioned by others. It seems that with all the various poses and procedures there would

<sup>1</sup> Case, James T.: Roentgenography of the Liver and Biliary Passages, with Special Reference to Gall Stones, Jour. Am. Med. Assn., vol. 61, No. 12, p. 920.

<sup>2</sup> Carman, Russell, D.: Roentgen Diagnosis of Diseases of the Alimentary Canal, W. B. Saunders Company, Philadelphia, 2d ed., 1921, p. 425.

<sup>3</sup> Nichols, B. H.: Application of X-rays in Diagnosis of Gall-bladder Diseases, Surg. Clin. North America, 1924, 4, 921.



be the occasional rare instance in which it would be impossible to decide on the nature of a shadow found in this locality.

The second period of development of the roentgen-ray examination of the biliary tract closes with a high degree of efficiency for



FIG. 94

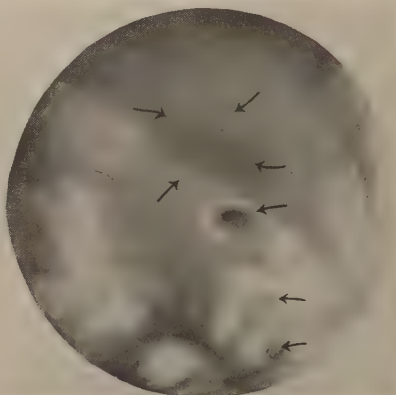


FIG. 95

FIGS. 94 and 95.—Fig. 94: Intra-abdominal calcification of unknown nature, thought to be gall stones, eliminated from consideration by the gall bladder image seen above. Fig. 95: Fecaliths; above large laminated gall stone is indicated by arrows.

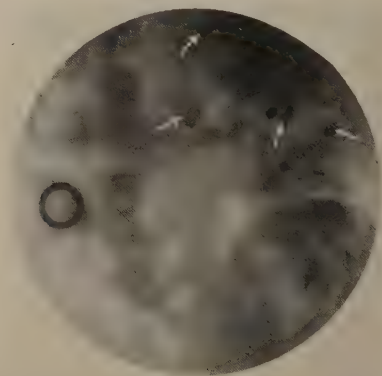


FIG. 96.—Barium collected in diverticula of colon.

ordinary roentgen-ray methods, due to the splendid work done by L. G. Cole, George, George and L. G. Cole, George and Leonard, Pfahler, Case, Kirklin, Arens, the late R. W. Mills, and many other Americans, and by Holland and Knox in Great Britain, and Haenisch in Germany.



FIG. 97.—Diagrammatic representation of intra-abdominal calcification, drawn from radiographs. 1 to 6, urinary calcifications; 7, calcified costo-chondral junction; 8, portion of calcified costal cartilage (note the angle of its long axis); 9, calcified abdominal lymph node; 10, calcified fecalith.



FIG. 98.—Diagrammatic representation of opaque gall stones, drawn from radiographs. 1, multiple stones; 2, single large stone with light center; 3, single homogeneous stone; 4, multiple gall stones; 5, multiple gall stones, with patient prone; 6, the same, with patient erect; 7, multiple small stones; 8, "ring" stone; 9 and 10, multiple "ring" stones; 11, multiple stones; 12, multiple stones, visualized through a fetal head in a case of breech presentation.

**Essential Points in Gall-tract Radiography.**—The methods and technique of roentgen-ray examination of the biliary tract, and its interpretation, are so well covered by the works of George and Leonard,<sup>1</sup> Knox,<sup>2</sup> Manges<sup>3</sup> and Haenisch<sup>4</sup> that they will be omitted from this volume. It should be stated, however, that certain points which these writers emphasize merit repetition because of their great importance. The roentgen-ray examination for biliary-tract disease should be an integral part of a complete radiographic gastrointestinal study. Every means should be used to secure technical excellence in the films which must be employed. We believe with those writers that the finer changes brought about by disease cannot possibly be observed on the fluoroscopic screen. In order to secure technically excellent films, the method of trial and error so strongly urged by George and Leonard<sup>5</sup> is the only one that will be uniformly successful. This means the making of exposures until the optimum quality for the given patient is obtained, the patient remaining at hand for additional raying if it becomes necessary.

## SECTION II.

### DISCUSSION OF THE VALUE OF ROENTGEN-RAY EXAMINATION OF THE BILIARY TRACT PRIOR TO CHOLECYSTOGRAPHY.

**The Radiological Signs of the Pathological Gall Bladder.**—The roentgen criteria which establish disease of the gall bladder, as has been said, consist in the demonstration of certain direct and indirect signs. The surest of these is the finding of biliary calculi. When their presence is revealed, in spite of much contrary opinion and the often repeated statement that every tenth person has gall stones, it does seem that W. J. Mayo's<sup>6</sup> belief that there are no innocent gall stones should guide one in concluding that there is an abnormal condition in the biliary tract. If that is granted, then the presence

<sup>1</sup> George, A. W. and Leonard, R. D.: *The Pathological Gall Bladder*, Paul B. Hoeber, Inc., New York, 1922.

<sup>2</sup> Knox, Robert: *Radiography in the Examination of the Liver, Gall Bladder and Bile-ducts*, C. V. Mosby Company, St. Louis, 1921.

<sup>3</sup> Manges, W. F.: *Non-surgical Drainage of the Gall Tract*, Lyon, Lea & Febiger, Philadelphia, 1923, chap. xx, p. 377.

<sup>4</sup> Haenisch, F.: *Röntgendiagnostik der Gallensteine und der Gallenblase ohne Kontrastmittel*, Fortschr. auf dem Gebiete der Röntgenstrahlen, 1927, **35**, 177.

<sup>5</sup> George, A. W. and Leonard, R. D.: *The Pathological Gall Bladder*, Paul B. Hoeber, Inc., New York, 1922.

<sup>6</sup> Mayo, William J.: "Innocent" Gall Stones a Myth, Jour. Am. Med. Assn., 1911, **56**, 1021.



of stone is the most reliable roentgen-ray sign of gall-bladder disease that we have.

The second direct sign, namely, the demonstration of a gall-bladder image, is of far less reliability than the preceding. Several writers have claimed that it can be shown in normal subjects, and therefore this sign is of little use. Of course, in those rare cases of calcification of the gall-bladder wall its roentgen-ray visualization is of the greatest value. The indirect signs consist of fixation and displacement, and less frequently deformity, of the structures of the right upper quadrant, and are strong corroborative evidence of an antecedent inflammatory process which has involved the peritoneal coats of the structures in that locality. The other secondary sign,



FIG. 99.—Spasm of stomach and duodenum, indicated by arrows. There was also retardation of the opaque meal in the duodenum.

the behavior of the opaque meal in relation to movement and spasm in the stomach and duodenum (Fig. 99), may occur from so many other causes than disease of the gall bladder and may be lacking in known cases of involvement of that organ, that it appears to us as being valueless in reaching a conclusion. It would appear that such signs would accompany chronic duodenal ileus or stasis, chronic duodenitis, or duodenal diverticulum, rather than cholecystic disease. These conditions have attracted attention comparatively recently and are not yet completely understood. Abnormal behavior of the opaque meal would be anticipated with them. This coupled with the fact that *symptomatically* chronic cholecystitis and these conditions of the duodenum are almost impossible of differentiation, are the reasons why these signs have received the prominence they have

had in the past. Should a fistula exist between the vesicle and any portion of the alimentary tract it might become filled by the opaque meal. If found, it is of course sure evidence of gall-bladder disease. George and Leonard<sup>1</sup> claim that a portion of the barium meal may enter and be retained for hours in the ampulla of Vater, but not in normal individuals. They therefore consider this finding pathognomonic of biliary tract or pancreatic disease.

**Evaluation of Radiological Diagnosis in the Biliary Tract.**—The correctness of radiological diagnosis based on a combination of part or all of these signs is given at various percentages by various observers. L. G. Cole<sup>2</sup> found that 80 per cent of gall stones submerged in bile cast a shadow less dense than this medium, and thought that this would indicate that only 20 or 25 per cent of stones could be shown. However, he thought that cholesterol stones were so much less dense than bile that they would, as they often do, appear as the so-called "negative" stones. His article is a most complete and thorough roentgen-ray study of the composition of gall stones. Pfahler,<sup>3</sup> in the same year, claimed 74 per cent of positive findings of pathological gall bladder, though expressing his belief that only 50 per cent of stones are demonstrable. George and Leonard<sup>4</sup> claim 88.4 per cent correctness, and Arens<sup>5</sup> and Kirklin<sup>6</sup> approximately the same. These writers include both the direct and indirect signs of gall-bladder disease in the foregoing statements; in other words, the figures apply to diagnosis of pathological condition in the biliary tract, and not to the finding of gall stones alone. George and Leonard,<sup>7</sup> Case, and Dodd, quoted by Case,<sup>8</sup> hold that inspection and palpation at operation will not rule out disease of the gall bladder, hence as a measure of accuracy of roentgen-ray examination they are insufficient, a point which will be referred to again. A composite opinion of those who have written on the subject indicates that the roentgen-ray examination to determine

<sup>1</sup> George, A. W. and Leonard, R. D.: *The Pathological Gall Bladder*, Paul B. Hoeber, Inc., New York, 1922.

<sup>2</sup> Cole, L. G.: *Detection of Pure Cholesterol Gall Stones*, *Am. Jour. Roentgenol.*, 1914, **2**, 440.

<sup>3</sup> Pfahler, George E.: *Roentgen Rays in the Diagnosis of Gall Stones and Cholecystitis*, *Jour. Am. Med. Assn.*, 1914, **62**, 1304.

<sup>4</sup> George, A. W. and Leonard, R. D.: *Roentgen Diagnosis of Pathological Gall Bladders*, *Am. Jour. Roentgenol.*, 1917, **4**, 321.

<sup>5</sup> Friedman, J. C., Strauss, A. A. and Arens, R. A.: *A Clinical Radiological Study of the Gall Bladder*, *Radiology*, August, 1925.

<sup>6</sup> Kirklin, B. R.: *A Plea for the Routine X-ray Examination of the Gall Bladder Region in Every Chronic Abdomen*, *Radiology*, 1924, **2**, p. 227.

<sup>7</sup> George, A. W. and Leonard, R. D.: *Ibid.*

<sup>8</sup> Case, James T.: *Roentgenography of the Liver and Biliary Passages*, with Special Reference to Gall Stones, *Jour. Am. Med. Assn.*, vol. **61**, No. 12, p. 920.

the presence of disease in the biliary tract reached a high order of efficiency. Case,<sup>1</sup> in an elaborate study concludes in a conservative tone that gall stones can be demonstrated in 50 per cent of the cases he examined, and a pathological gall bladder, with or without stones, in 88 per cent. These figures, however, are misleading as consideration is not given to the type of case examined, and whether such examination was instituted by a desire to confirm a clinical impression of a pathological gall bladder, or whether they were routine examinations of the alimentary tract of patients with indefinite symptoms which might be referable to any portion of it. Naturally, if a large series of cases is examined to confirm a clinical impression of gall stones, a large number of them will be found.

In relation to the findings of stones and to a somewhat less degree to the secondary evidence of biliary tract disease, it must be borne in mind that heavy subjects may be examined with a negative result, which is due entirely to the thickness of body through which the examination has to be made. This has a bearing on present-day methods, though this difficulty has been decreased to some extent by the employment of the Potter-Bucky diaphragm in obese and heavy individuals.

Simple roentgen-ray examination of the biliary tract has had and still has a great field of usefulness, but there are several points of weakness in it which need to be discussed. The fundamental consideration in disease of this tract is the matter of infection and, second, and of only slightly less importance, the results of such infection. In other words, cholecystitis (with or without stones) or pericholecystitis, being the conditions demanding treatment, are the ones which need to be discovered.

**Defects of Simple Radiography of the Biliary Tract.**—Aschoff<sup>2</sup> is of the opinion that gall stones originate in two ways: (1) As a result of infection of the gall bladder, which produces stones, the chief components of which are pigment and calcium; (2) through some obscure chemical process which results in the production of the "pure cholesterol stone." The latter type, through its properties as a foreign body, in the course of time creates a condition upon which infection supervenes with concomitant calcium deposition on its periphery. Through experience with cholecystography, one of the writers<sup>3</sup> independently arrived at the same conclusion. In

<sup>1</sup> Case, James T.: Some Statistics on the Negative and Positive Roentgen Diagnosis of Gall Stones, *Am. Jour. Roentgenol.*, 1916, **3**, 246.

<sup>2</sup> Aschoff, L. and Bacmeister, A.: *Die Cholelithiasis*, Verlag von Gustav Fischer, Jena, 1909.

<sup>3</sup> Moore, S.: Cholecystography: A Summary—read before the Twelfth Annual Meeting of the Radiological Society of North America, at Milwaukee, November 28 to December 4, 1926, in press.

either case, such stones, when demonstrable by ordinary methods, have been in existence for a material length of time and much damage may have been done to the gall bladder and possibly to adjacent and related structures. It is therefore highly desirable that they should be dealt with before they have attained those characteristics which render them discoverable on roentgen-ray examination. Furthermore, cholecystitis of all degrees of severity and chronicity can and does exist in the absence of gall stones either with or without calcium.

In regard to the other direct sign of gall-bladder disease, viz.: the demonstration of a gall-bladder shadow, whatever one's views may be in regard to it, it must be conceded that to achieve a thickening of the gall-bladder wall sufficient to have it appear in a radiograph, a long-standing inflammation must have been precedent. On the other hand, extensive inflammation of the gall bladder of considerable duration may occur, and at examination of the excised organ its wall will be so little thickened that such change is unrecognizable by the palpating finger. Naturally it is unreasonable to suppose that it would be disclosed radiographically. Whether there might be an increased density of the gall bladder because of increased density of its contents, aside from stones or calcareous mural deposit, is debatable. Lewald<sup>1</sup> claims an over-concentration of the bile in a case in which stones were observed because of their relatively lesser opacity. He attributed this result to over-absorptive capacity of the gall bladder. Over-concentration in relation to cholecystography has recently been suggested to the writer by Kirklin (personal communication), and this, coupled with repeated mention of "dark," "tarry," "inspissated," "thick," "black bile," as evidence of gall-bladder disease, leads to the belief that possibly dense gall-bladder bile might produce a radiographic gall-bladder image. However, experience with cholecystography and observation of bile such as described under these terms lead to the belief that most of these types of bile are undoubtedly normal. On theoretical grounds, the thickest, most dense, tenacious bile should be found in cases of hydrops of the gall bladder, for here there is bile retention in a structure with a concentrating mechanism. Possibly this occurs in the early stages of the obstruction and as a transitory phase, but the contents of the hydropic gall bladder are certainly more fluid than the normal concentrated gall-bladder bile. It is difficult to reconcile this with an hypothetical over-concentra-

Lewald, L. T.: Discussion, Radiology, 1925, 4, p. 87.



tion. However, it seems that this supposititious sign of gall-bladder disease may be present with a normal organ.

Displacement, fixation and distortion of the structures of the right upper quadrant disclosed by the opaque meal are produced by adhesions, and constitute indirect signs of gall-bladder disease of much value. They can also be shown by cholecystography, which fact will be more fully dealt with further on. As has been already mentioned, these deformities are the result of a localized peritonitis in this region, which might have been initiated by disease of the gall bladder. Schürmayer<sup>1</sup> was the first to appreciate the significance and to analyze the origin of such findings. According to him, they arise from two sources: the pericholecystitis of cholelithiasis and disease of the liver, and the pericholecystitis of ulcer of the stomach and duodenum. The latter class should embrace pathological conditions in addition to ulcer. Since gall-bladder disease is far more frequent than that of the duodenum and stomach, adhesions in the right upper quadrant probably most commonly originate from it. Radiological opinion indicates a belief that fixation, distortion, etc., are exclusively of gall-bladder origin. We can conclude, however, that only a proportion of patients having these findings begin with cholecystic disease. Finally, their demonstration is after all rather infrequent. Taken in conjunction with the fact that adhesions about the gall bladder are very frequently found at operation in cases of cholecystitis, then their importance sinks into relative insignificance when reaching a conclusion as to disease of that viscus. A considerable lapse of time is required to produce adhesions which will distort, displace, and fix the organs in question. They are sequels of infection of this region that should be prevented through early diagnosis if the means are at hand for doing so. When adhesions have formed and are of such extent that they are recognized by the opaque meal, chronic inflammation is to be inferred. If found, either with simple roentgen-ray methods or by means of cholecystography, whatever the origin may be, the probabilities are that they will give rise to symptoms of such severity that surgical intervention is demanded. However discovered, we may consider them as a late and unreliable sign of cholecystitis.

Since the discovery of cholecystography, the other indirect manifestations of gall-bladder disease, namely, impressions upon

<sup>1</sup> Schürmayer, C. B.: Pathologische Fixation bzw. Lagveränderung bei Abdominalorganen und die röntgenologische Diagnostik, Fortschr. auf. dem Gebiete der Röntgenstrahlen, 1910, 15, 308.

the duodenal bulb or antrum of the stomach, have been shown to occur in normal subjects. (Case,<sup>1</sup> Moore.<sup>2</sup>) (Figs. 100 and 101.) These impressions, to which Manges,<sup>3</sup> George and Leonard,<sup>4</sup> Arens,<sup>5</sup> Haenisch,<sup>6</sup> and others attach some importance as indicating a tense and enlarged, and therefore diseased, gall bladder (including hydrops), are much decreased in value. The mere discovery of one of these is also to be rejected unless it persists when attempts are made to dislocate the stomach or duodenum away from the imprinting structure, allowing them to fill with the opaque meal. Cholecystography reveals such a wide range of position, size and shape of

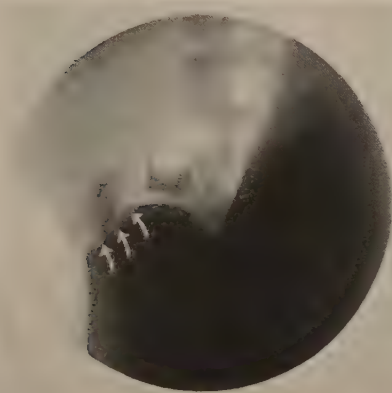


FIG. 100

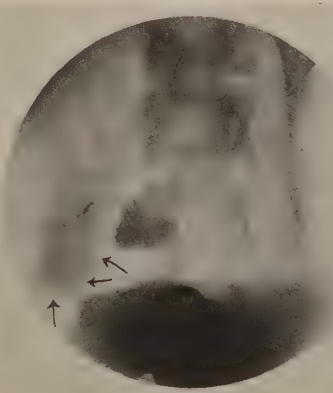


FIG. 101

FIGS. 100 and 101.—Fig. 100: Arrows indicate a supposed impression of gall bladder on the antrum of stomach. Fig. 101: Cholecystogram is indicated by arrows. Normal gall bladder.

the visualized gall bladder that one is led to believe that these impressions may be and probably frequently are the imprints of intestinal coils brought into abnormal relationship through disease in this region, independent of that of the gall bladder.

<sup>1</sup> Case, James T.: The Relative Value of Cholecystography and the So-called Direct and Indirect Methods of Radiologic Examination of the Gall Bladder, *Am. Jour. Roent. and Rad. Ther.*, 1926, vol. 16.

<sup>2</sup> Moore, S.: The Development and Application of Cholecystography, *Brit. Jour. of Radiol.*, August, 1926.

<sup>3</sup> Manges, W. F.: Non-surgical Drainage of the Gall Tract, Lyon, Lea & Febiger, Philadelphia, 1923, Chap. XX, p. 377.

<sup>4</sup> George, A. W. and Leonard, R. D.: The Pathological Gall Bladder, Paul B. Hoeber, Inc., New York, 1922.

<sup>5</sup> Friedman, J. C., Strauss, A. A. and Arens, R. A.: A Clinical Radiological Study of the Gall Bladder, *Radiology*, August, 1925.

<sup>6</sup> Haenisch, F.: Röntgendiagnostik der Gallensteine und der Gallenblase ohne Kontrastmittel, *Fortschr. auf. dem Gebiete der Röntgenstrahlen*, 1927, 35, 177.

**Statistics of Gall-bladder Radiology Before Cholecystography.**—

In the roentgen-ray department of the Barnes Hospital from the time of its opening in 1914 to the advent of cholecystography, there were 4040 roentgen-ray examinations of the alimentary tract and 261 of the gall bladder. Among these calculi were demonstrated in 85 cases. The secondary signs of gall-bladder disease had little importance attached to them. Possibly our skill in their demonstration and interpretation was not equal to that of others engaged in this work. A factor influencing the discovery of some of these secondary signs with the opaque meal is the fact that our gastro-intestinal examinations, unless precluded by the patient's condition, were made in the erect posture. Displacement and fixation of the stomach and duodenum, therefore, would probably not be shown, certainly not so readily as would be the case were examinations made in the prone posture. Of 152 cases reported with gall-bladder disease, with or without stones, 89 were operated on and the radiological diagnosis was correct in 67.1 per cent of them. Over the same period there were 332 operations on the gall bladder. In these cholecystitis alone was found in 124 cases, and with stones 208 times. (These figures should be contrasted with those on pages 314 and 315.) There are certain conclusions that may be drawn from these figures: (1) Though the clinicians had immense faith in the radiological examination of the gastro-intestinal tract, they had very little in that part of it pertaining to disease of the gall bladder. (2) Where the most reliable direct sign of gall-bladder disease was elicited, it proved correct in a high percentage of cases operated on. (3) Most of the operated cases were clinically sufficiently clear or severe to warrant omission of a roentgen-ray examination. (4) Only about 63 per cent of the cases of cholecystitis had stones, and in a material proportion these must have been of pure cholesterol composition. These figures therefore indicate that in spite of faithful effort made in that direction when it was desired, ordinary roentgen-ray methods of examination of the biliary tract were of a very low order of efficiency.

**The Worth of Simple Radiography of the Biliary Tract.**—In closing the discussion of the roentgen-ray examination of the biliary tract of this period, it is clear that though of great value on some occasions and in some cases, a means or method for earlier diagnosis was desired.

Except for a small amount of information in regard to its position and, to some extent, the character of the upper border of its right lobe, roentgen-ray examination reveals little in regard to the liver.

Even in respect to its size and position, the roentgen-ray findings are quite inconstant, depending as they do on the visualization of its lower border, which is not easily accomplished, because of the lack of contrast in density of the abdominal structures. It is rarely observed in films of stout individuals. Pfahler<sup>1</sup> has recently applied radiography to the study of the dimensions of the liver. Unfortunately, he did not correlate height, weight and habitus with liver size. As far as this gland is concerned, radiology is of little value in demonstrating its deviations from the normal.

Knowledge in respect to the ducts of the biliary system, gained by roentgen-ray examinations, is only slightly less meager than that of the liver. Such as there is chiefly inferential in nature and is deduced from the clinical facts or physical findings. For example, in the presence of obstructive jaundice, a visualized gall stone can probably be taken as lying in the common duct. If hydrops of the gall bladder can be determined and a gall stone is visualized in the roentgen-ray film, one can safely conclude that the calculus is in the cystic duct. In conclusion, it may be said that even with modern methods, *i. e.*, cholecystography, the liver and the bile-ducts are rather sterile fields for roentgen-ray procedures. In the biliary tract the value of the latter is almost confined to the study of the gall bladder.

In point of fact, the efficiency of ordinary radiographic examination is to be attributed to the personal skill and ability of a few men. This has been of such high degree that the method was certainly not useful in the average institution, nor by the average radiologist. Discontent with the unsatisfactory situation led to the development of the third phase of roentgen-ray gall tract diagnosis.

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### SECTION III.

#### THE DEVELOPMENT OF CHOLECYSTOGRAPHY, ITS PRINCIPLES AND TECHNIQUE.

**General Remarks.**—The preceding section makes it clear that not only did radiography give a high percentage of diagnostic error but the Barnes Hospital figures suggest that in many instances the pathological gall bladder may elude detection through this means.

<sup>1</sup> Pfahler, George E.: The Measurement of the Liver by Means of Roentgen-rays, Based upon a Study of 502 Subjects, *Am. Jour. Roent. and Rad. Ther.*, 1926, vol. 16, No. 6.



Further in its disfavor, as has already been said, is the fact that the roentgen-ray findings reveal the effects of chronic disease. Surgical endeavor has generally been interested in earlier diagnosis of gall-tract involvement, for the reason that late intervention, aside from the greater attendant difficulty and hazard, gives results which are unfavorable in ratio to the degree of pathological change that has ensued. Gall-tract radiography was of limited value to the surgeons even when supported by the developments and methods outlined in Sections I and II. If it can be said that there is such a thing as the medical treatment of gall-bladder disease, radiology has contributed nothing to it. The third and present era of the radiology of the vesicle and ducts originated from dissatisfaction with the available diagnostic means.

**Fundamentals of Contrast Media.**—As has been stated by many writers, radiography is a “study of contrasts in density.” Realization of this has, from the earliest days of roentgen-ray applications, led investigators to seek means for enhancing contrasts or generating them where they are non-existent. In general these efforts have consisted of filling hollow structures or body cavities with a contrasting substance of a greater or lesser density than their surroundings. As is well known, this gives a vast amount of valuable information in regard to the size, capacity, outline, and relationship of structure submitted to such manœuvres. What is not so well known, and therefore warrants attention, is the almost strictly anatomical nature of knowledge so obtained and the meager physiological information revealed, except as regards contractions of intrinsic muscles. Another consideration which it is well to mention is that in the two most important fields in which this method is used, the gastro-intestinal and urological, the ingress of the contrasting substance is by way of the natural surface openings, and that it is here that practically all estimate of function is to be gleaned from these procedures. Where artificial openings exist or have to be made for the introduction of contrast media, relatively no physiological information is obtainable.

**The Basis of Cholecystography.**—Graham and W. H. Cole,<sup>1</sup> in 1923, conceived the idea that if the gall bladder could be rendered visible by the roentgen-ray after being filled with a contrasting substance, “not only might earlier and more certain signs of pathological change in that organ be made recognizable, but also such a

<sup>1</sup> Graham, E. A. and Cole, W. H.: Roentgenologic Examination of Gall Bladder; Preliminary Report of a New Method Utilizing Intravenous Injection of Tetra-bromphenolphthalein, *Jour. Am. Med. Assn.*, 1924, **82**, 613.

procedure might be a more accurate index of function of both liver and gall bladder." (Figs. 102 to 105.) In order to attain this, all known means and procedures in producing artificial contrasts

FIG. 102

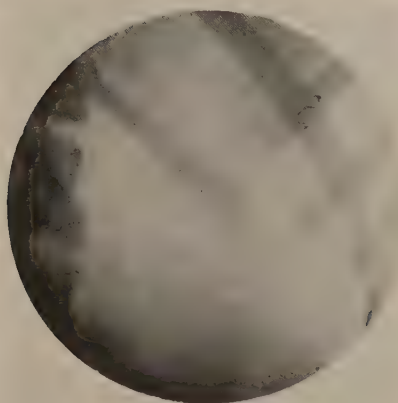


FIG. 103

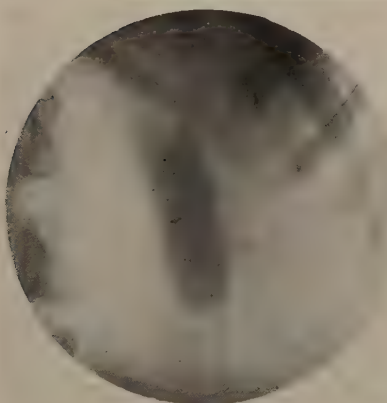
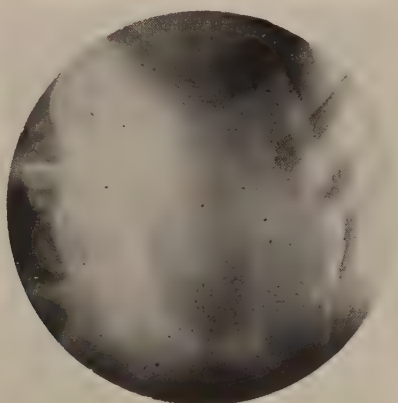


FIG. 104

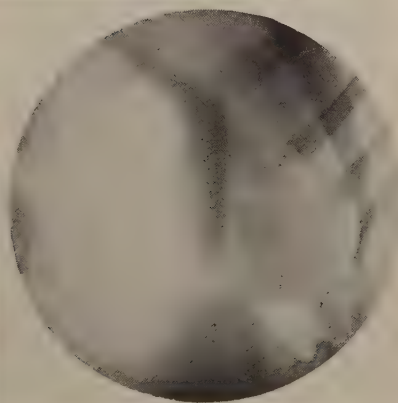


FIG. 105

FIGS. 102, 103, 104 and 105.—First successful cholecystogram in the human. Fig. 102: Four hours after injection of sodium tetrabromphenolphthalein; gall-bladder image not observed in reproduction; is seen faintly in Fig. 103. Fig. 104: Greater density at twenty-four hours. Fig. 105: At thirty-two hours. Persistence of shadow to be attributed to prolongation of starvation period which was carried out at that time.

had to be departed from, and they struck out into a new field. The experimental work and underlying theory which led up to the discovery of cholecystography is dealt with in Chapter III. It

suffices to say that from the radiological standpoint the problem of visualizing the gall bladder differs in nearly every respect from that demanded for the development of any of the other artificial contrasts. It embodies an entirely new and original radiological principle, namely, the utilization of the specific functions of a system to engender a difference in density. Cholecystography is therefore largely a test of physiological capacity in contradistinction to the almost wholly mechanistic nature of the opaque-meal examination, pyelography, etc. Very early in our experience we learned that cholecystography was quite narrowly limited in the amount of anatomical (in this term lithiasis is embraced) change it was capable of disclosing, and we came to rely on it as a measure of function. From this, anatomical (pathological) conditions can be deduced.

**Physiological Principles of Cholecystography.**—In the chapter on Physiology, it is shown how the dyes employed in cholecystography are excreted by the liver, reach the gall bladder in small but increasing quantities, mix with the bile there present, and become concentrated to the point where they make the vesicle opaque to the roentgen-rays. After the lapse of about twenty hours (depending on quality and frequency of food intake), the dye-containing bile begins to disappear and, in normal cases, at the end of twenty-four hours and on resumption of usual diet, the gall bladder can no longer be visualized. The preceding is a repetition of what has already been said elsewhere. It is justified, however, because there is a definite cycle for the behavior of cholecystographic media, and hence the periods for radiographic examination are predetermined. By observation and experiment we found that for the normal individual these were at four, eight and twenty-four hours after the intravenous injection. If alimentary administration is resorted to, we follow approximately the usage of Menees and Robinson,<sup>1</sup> Stewart and Ryan,<sup>2</sup> and others, making the examinations at fifteen, nineteen, and twenty-three hours following the ingestion of the dye. This routine is departed from in the pathological cases if the findings indicate that this may be done to advantage. Such modification is most commonly in the direction of an increase in the number of films made either by shortening the intervals between them or, as is most frequently the case, prolonging the examination to later hours. Naturally, if those influences which may void the examina-

<sup>1</sup> Menees, T. O. and Robinson, H. C.: Oral Administration of Tetraiodophenolphthalein for Cholecystography, *Radiology*, 1925, **5**, 211.

<sup>2</sup> Stewart, W. H. and Ryan, Eric J.: Reliability of Cholecystography by the Oral Method as Shown by an Analysis of One Hundred Consecutive Cases, *Am. Jour. Roent. and Rad. Ther.*, 1926, vol. **16**, No. 3.

tion have been brought into play, the examinations are desisted from. These are, in the intravenous cases, injudicious eating or incomplete injection, and in the alimentary, premature loss of the dye, either by the stomach or bowels. It may be said here that the rectal and intraduodenal administration methods have been virtually abandoned by all workers in this diagnostic field. Deviations from the foregoing practice invite failure though it appears that decreased bodily activity may have a modifying effect on the excretion of the dye and the behavior of the dye-filled gall bladder, so that the time of the first examination may be advanced beyond four hours. Case<sup>1</sup> injects his patients in the late afternoon, the first film being taken the following morning. On the other hand, usual activity does not appear to increase the rate of filling, concentrating or emptying of the gall bladder, as far as we were able to determine in a large number of ambulatory patients. (Moore and Gay.<sup>2</sup>)

No less definite and of even greater importance than physical activity, in regard to success or failure, is the matter of food intake, its importance warranting another repetition. The reason why food may and does nullify a cholecystographic examination is shown also in the chapter on Physiology. In examining cholecystograms, when one finds a usual gall-bladder image at four hours and none, or a fainter one, at eight hours, suspicion of unwise eating should be at once aroused and the test should be repeated.

**Cholecystography and the Fat Meal.**—The visualized gall bladder alters in size, being largest at some period between the eighth and twelfth hours after the dye reaches the circulation, becoming smaller from that period onward. These changes throw light on the elasticity or flexibility of the gall-bladder wall. The measure of this property has been extended by other workers. Whitaker,<sup>3</sup> making use of Boyden's<sup>4</sup> observation on the emptying of the gall bladder of the cat on the ingestion of the yolk of egg and fats, applied it clinically to the visualized vesicle and found that shortly after the ingestion of fat the gall-bladder shadow decreases greatly in size. For this to take place the walls of the viscus must be free from that rigidity which would be produced by infiltration or fibrosis conse-

<sup>1</sup> Case, James T.: The Relative Value of Cholecystography and the So-called Direct and Indirect Methods of Radiologic Examination of the Gall Bladder, *Am. Jour. Roent. and Rad. Ther.*, 1926, vol. **16**, No. 3.

<sup>2</sup> Moore, S. and Gay, L. P.: Cholecystography, with Special Reference to its Employment on Ambulatory Patients, *Southern Med. Jour.*, 1926, **19**, 109.

<sup>3</sup> Whitaker, L. R.: The Mechanism of the Gall Bladder, *Am. Jour. Physiol.*, 1926, vol. **78**, No. 2.

<sup>4</sup> Boyden, E. A.: The Effects of Natural Foods on the Distension of the Gall Bladder, etc., *Anat. Rec.*, 1925, **30**, 333.



quent to infection. This fat meal test of the visualized gall bladder has been widely accepted and is reputed to be most valuable in cholecystography. We have not made use of it to any great extent, as we prefer to estimate this property of the viscus under as nearly normal conditions as the starvation period and the resumption of ordinary diet permits. Our experience with cholecystography warrants us in holding the thesis that if the gall bladder is visualized its coats are not inelastic, and as a corollary, that a pathological process sufficient to produce an inelastic wall is incompatible with the preservation of the concentrating function of the organ. This view is opposed to that of many other observers. Sosman,<sup>1</sup> Mateer and Henderson<sup>2</sup> are of the opinion that sometimes stones may be present in a dye-filled gall bladder which can only be rendered visible when a decrease in size of this organ has occurred through the administration of this meal. The former also believes that its omission will lead to the non-discovery of many cases of stones. As will appear further on, our ideas on this point are different.

**General Rules of Cholecystographic Technique.** — In simple radiographic examination of the gall bladder, without contrast media, satisfactory results are to be attained only with the most exacting technique. There have been objections from the masters of this art, that cholecystography might be considered a ready means of diagnosing the pathological gall bladder, applicable with ease by anyone possessing roentgen-ray equipment; in a word, that some might have the opinion that it is a simplified, ready-made, universally applicable procedure. Nothing could be further from the truth than this belief. The technique necessary for success in cholecystography is of the highest order. The roentgen-ray technique of cholecystography varies in detail with virtually everyone having recourse to it, but the general principles are quite constant for all workers. The object should be to secure the optimum technical quality of the films for a given subject. To insure this, immobility of the patient, rapid exposure, re-raying when necessary, covering of all zones in which the gall bladder might be situated, and attention to the details of development of the films, are essential in order that one may have cholecystograms of the finest quality. Position of the patient is of much importance, and the standard pose employed by most workers is with the patient prone, and the dorso-ventral

<sup>1</sup> Sosman, M. H.: Discussion of "Cholecystography: A Summary" (S. Moore), read before the Twelfth Annual Meeting of the Radiological Society of North America, at Milwaukee, November 28 to December 4, 1926, in press.

<sup>2</sup> Mateer, J. G. and Henderson, W. S.: Chronic Biliary Tract Disease, Arch. Int. Med., vol. 33, No. 6, p. 728.

direction for the rays. This is deviated from under certain circumstances. Occasionally a patient cannot assume the prone position; in that event the raying may be done in the opposite direction, though it is unsatisfactory. There is the occasional unusual case, which one learns from experience, that requires filming with the patient lying on the right side. This will always give valuable information as to the location of the organ in relation to the coronal plane. The posterior-anterior raying in the upright position is invaluable and cannot be dispensed with in certain cases of high or bizarre location of the gall bladder, those cases, in other words, which in the prone posture suggest fixation of the gall bladder in unusual positions, through adhesions. There is also much to be learned from this pose in cases in which there is doubt as to a pendulous, unusually long, flexible gall bladder. In covering all the zones in which this organ may be found, if the radiologist will give due attention to the type of habitus of the patient, this search may be made with more ease than might be anticipated.

Preparation of the patient is unnecessary as a prerequisite to cholecystography except to insure that gastric digestion is not proceeding a few hours before and eight hours after the intravenous injection of the dye. In alimentary administration the dye is given with the evening meal of the day preceding the examination. In neither method should laxatives be used as a preparatory measure. They may give rise to conditions that would alter the cholecystographic behavior of the gall bladder. However, there are some workers who recommend a mild laxative twenty-four hours before the dye is given; others believe that a preliminary fat meal will, by emptying the gall bladder, prove advantageous. (Stewart.)<sup>1</sup> Some of the German workers administer pituitrin to attain the same end, the idea being that if the gall bladder is empty when the dye-laden bile reaches it, the function of concentration may be more accurately observed. In this connection, and because it might lead to unwise measures, it may be said that intestinal gas collected in the gall-bladder region is most troublesome in interpretation. We have been unsuccessful so far in dealing with it by enemas.

**Detailed Technique.**—Many workers use a single large film for their cholecystograms, in this way insuring complete covering of all possible gall-bladder sites. This is done with a certain amount of sacrifice of detail. Our practice consequently is to use a smaller

<sup>1</sup> Stewart, W. H. and Ryan, Eric J.: Reliability of Cholecystography by the Oral Method as Shown by an Analysis of One Hundred Consecutive Cases, *Am. Jour. Roent. and Rad. Ther.*, 1926, vol. 16, No. 3.

film with smaller diaphragm and cover the field to be investigated with several exposures. Our choice of technique is the following: For the patient of average thickness: target film distance 25 inches; a double intensifying screen with duplitized film;  $3\frac{1}{2}$ -inch spark gap; 60 to 80 milliamperes of current, and exposure time as short as it can be made. A cone of 5-inch diameter is invariably used. Because of the lack of rapidity, and as we believe there is some vibration from it, our preference is not to use the Potter-Bucky diaphragm, except in the very heavy subject or for exposure in the lateral position. Dark-room technique should be precise and careful attention should be given to all its details.

The dye-filled gall bladder can be observed on the fluoroscopic screen. However, the observation of Buxbaum<sup>1</sup> applies with equal force here as it did in the case of gall stones. The finer changes discoverable in a cholecystogram escape detection on the screen. However, screening in conjunction with the barium meal, when the two procedures are carried out synchronously, may give invaluable information in regard to the stomach and duodenum. This is true also of the colon and the barium enema.

#### SECTION IV.

#### THE SUBSTANCES USED IN CHOLECYSTOGRAPHY AND THE TECHNIQUE OF THEIR ADMINISTRATION.

SINCE the introduction of cholecystography by us<sup>2</sup> in 1924, numerous variations and modifications have been suggested by various authors in an endeavor to simplify the method and enhance its value. Our original work was started with the sodium salt of tetraiodophenolphthalein, but on account of an inconsistency in the toxicity, due to impurities in the original sample, we began the use of tetrabromphenolphthalein. Because of the higher atomic weight of the iodine compound, and its greater impermeability to the roentgen-ray, we<sup>3</sup> tried a more refined product a short time later, and found it to be of practically the same toxicity as the bromine

<sup>1</sup> Buxbaum, A.: *Über die Photographie von Gallenstein in Vivo*, Wien. med. Presse, 1898, **39**, 534.

<sup>2</sup> Graham, E. A. and Cole, W. H.: Roentgenological Examination of the Gall Bladder; Preliminary Report of a New Method Utilizing the Intravenous Injection of Tetrabromphenolphthalein, *Jour. Am. Med. Assn.*, 1924, **82**, 613.

<sup>3</sup> Graham, E. A., Cole, W. H. and Copher, G. H.: Cholecystography: An Experimental and Clinical Study, *Jour. Am. Med. Assn.*, 1925, **84**, 14; Cholecystography: The Use of Sodium Tetraiodophenolphthalein, *Jour. Am. Med. Assn.*, 1925, **84**, 1175.

compounds. Independently and practically simultaneously with a later article of ours, Whitaker and Milliken<sup>1</sup> about a year after our first article reported the comparative values of tetrabromphenolphthalein and tetraiodophenolphthalein, and the superiority of the latter because of the smaller dose required for the production of cholecystograms.

Among the substances which we have studied are the following:

- I. Halogenated Derivatives of Phenolphthalein Compounds.
  1. Tetraiodophenolphthalein.
  2. Tetrabromphenolphthalein.
  3. Octabromphenolphthalein.
  4. Dibromphenolphthalein.
  5. Diiodophenolphthalein.
- II. Halogenated Derivatives of Iso-phenolphthalein.
  1. Tetraiodo-iso-phenolphthalein.
- III. Halogenated Derivatives of Phthalein Compounds.
  1. Phenoltetrachlorphthalein.
  2. Phenoltetrabromphthalein.
  3. Phenoltetraiodophthalein.
  4. Tetrabromphenoltetrachlorphthalein.
  5. Tetrachlorphenoltetrabromphthalein.
- IV. Sulphonated Halogenated Derivatives of Phenolphthalein.
  1. Dibromphenolsulphonephthalein.
  2. Diiodophenolsulphonephthalein.
  3. Tetrabromphenolsulphonephthalein.
  4. Phenoltetrabromsulphonephthalein (bromsulphalein).
  5. Tetraiodophenolsulphonephthalein.
- V. Halogenated Derivatives of Resorcinolphthalein or Fluorescein.
  1. Fluorescein.
  2. Tetrabromfluorescein (eosin).
  3. Tetraiodoffluorescein (erythrosin).
  4. Tetrabromdichlorfluorescein (phloxin).
  5. Tetraiodotetrachlorfluorescein (rose bengal).
  6. Octaiodoffluorescein.
  7. Dibromoxymercurifluorescein (mercurochrome-220 soluble).
- VI. Halogenated Phthalate.
  1. Tetraiodophthalate.
  2. Tetrabromphthalate.

<sup>1</sup> Whitaker, L. R. and Milliken, G. A.: Comparison of Sodium Tetrabromphenolphthalein with Sodium Tetraiodophenolphthalein in Gall Bladder Radiography, Surg., Gynec. and Obst., 1925, 40, 17.



## VII. Miscellaneous.

1. Thymol-iodide.
2. Tribromphenol.
3. Hexamethylene-tetramine (urotropin) iodine compound
4. Arsphenamine.
5. Silver arsphenamine.
6. Carbamide tetrachloriodide.
7. Phenolphthalein.
8. Trypan blue.
9. Methylene blue.
10. Gentian violet.
11. Azo-rubin.
12. Brom-azo-rubin.
13. Amiodoxyl benzoate (ammonium salt of o-iodoxy benzoic acid).
14. Tribrom-phenyl-glycine.
15. Iodized Congo red.
16. Brominated benzopurpurin.
17. Dibromo-diiodo-benzopurpurin.
18. Dibrom-trypan blue.
19. Tetrabrom-Congo red.
20. Tetrabrom-benzidine.
21. Tetrabrom-diiodo-Congo red.
22. Iodized sodium glycocholate.
23. Iodized sodium taurocholate.

The salts of thirteen of these substances were shown to produce cholecystograms. They are, namely, tetraiodophenolphthalein, tetrabromphenolphthalein, octabromphenolphthalein, tetraiodo-isophenolphthalein, phenoltetrabromphthalein, phenoltetraiodophthalein, phenoltetrabromsulphonophthalein, tetrachlorphenoltetrabromphthalein, tetrabromphenoltetrachlorphthalein, tetrabromfluorescein, tetraiodotetrachlorfluorescein, tetraiodoffluorescein and octaiodoffluorescein. All of these, except four, had disadvantages which precluded their clinical use. These disadvantages consisted chiefly either of a too great toxicity or of a general staining of the tissues of the body.

Two of them, viz., phenoltetraiodophthalein and tetraiodophenolphthalein, were found to be far superior to any of the others as "contrast media" in cholecystography.<sup>1</sup> The former seems superior

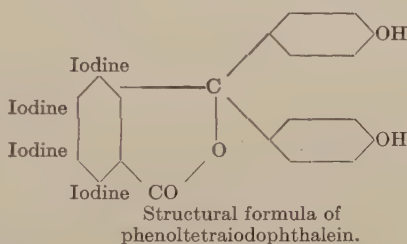
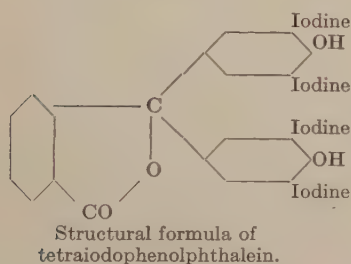
<sup>1</sup> These substances are manufactured and sold by the Mallinckrodt Chemical Works, St. Louis, under the name of "Iso-iodeikon" and "Iodeikon" respectively.

to tetraiodophenolphthalein because of the ability to stain the blood serum thereby allowing readings on the determination of hepatic function, increased rapidity of excretion by the liver, and because a smaller dose is required. Its simultaneous use in cholecystography and in the determination of liver function will be discussed elsewhere.

**Chemical Properties.**—Sodium tetraiodophenolphthalein has a molecular weight of 822. It is a light blue, crystalline compound, which is soluble in water to the extent of at least 40 per cent. It stains the blood serum only very slightly.

Phenoltetraiodophthalein is an isomer of the above compound, having the same molecular weight. Its crystals are dark violet in color and are soluble to about the same extent as tetraiodophenolphthalein.

The formulæ for the two compounds are as follows:



**Experimental Toxicity.**—Experimentally, the two drugs have practically the same toxicity. The lethal dose of 0.27 gm. per kilogram of body weight is five to seven times the dose used in human beings. We consider this margin absolutely adequate. The dose required to produce lesions in the liver, as found by Ottenberg and Abramson,<sup>1</sup> when they expressed the need for caution in the intravenous injection of tetrahalogen compounds, was four to six times larger than the dose per kilogram of body weight for cholecystography in man. We have found that a dose of 0.2 gm. per kilogram of body weight does not produce any lesion in animals, and it is highly improbable that the human dose, which is only one-fourth as large, would produce any pathological changes. On numerous occasions we have removed small pieces of liver at operation from human beings, and never have we seen any evidence of hepatic damage.

<sup>1</sup> Ottenberg, R. and Abramson, H. H.: Production of Liver Necrosis by Tetrachlorphenolphthalein and Tetrabromphenolphthalein, Jour. Am. Med. Assn., 1925, 84, 800.

On theoretical grounds, it would appear that obstruction of the common duct would greatly increase the toxicity of tetraiodophenolphthalein. Maddock and Whitaker<sup>1</sup> found, however, that animals which previously had had their common ducts ligated, would withstand 75 to 80 per cent of their estimated lethal dose. Of the many human beings with jaundice, due to common duct obstruction, which we have injected with tetraiodophenolphthalein and phenoltetraiodophthalein, we have not noticed any significant increase in toxic symptoms.

Pribram, Grünenberg and Strauss<sup>2</sup> report the administration of tetraiodophenolphthalein in a case of subacute yellow atrophy of the liver without the production of any significant reaction. A good shadow of the gall bladder was obtained.

**Intravenous Administration of Phenoltetraiodophthalein and Tetraiodophenolphthalein.**—As previously stated, we prefer the use of phenoltetraiodophthalein over tetraiodophenolphthalein, because of the smaller dose required and its ability to stain the blood serum.

To prepare phenoltetraiodophthalein for injection, 2.5 gm. of the dye are dissolved in 30 cc., or more, of freshly distilled water, with the aid of gentle heating, and the solution filtered through filter paper. The solution is then sterilized by boiling in a water-bath for fifteen or twenty minutes, and when cooled, is ready for injection. A convenient and safe way to keep the solution is to seal it in glass ampules in individual doses. Preserved in this manner, we have kept solutions for as long a time as two or three weeks, before using. Occasionally a slight precipitate will form on the bottom of the ampule, after the solution has been standing for a few days, but this has no indication of production of toxicity. If this precipitate is present, the solution should be either carefully withdrawn with a syringe, without mixing, or refiltered. The dose is 0.04 gm. per kilogram of body weight. However, it need not exceed 2.5 gm., regardless of the weight of the patient except in the extremely obese. The injection is done with a syringe and needle. The gravity method of introduction should quite certainly reduce the possibility of reaction, but at the present time we are not encountering enough reactions to warrant the use of the more complicated gravity method. The solution is injected all in one dose, in the morning, between 8 and

<sup>1</sup> Maddock, S. J. and Whitaker, L. R.: Effects of Sodium Tetraiodophenolphthalein in Complete Biliary Obstruction, *Boston Med. and Surg. Jour.*, 1926, 194, 973.

<sup>2</sup> Pribram, B. O., Grünenberg, K. and Strauss, D.: Die röntgenologische Darstellung der Gallenblase und ihre klinischepraktische Bedeutung, *Deutsch. med. Wchnschr.*, 1925, 11, 1429.

9 A.M., with the stomach empty and with the patient lying down. Care should be taken to establish a free flow of blood through the needle from the vein before introducing the dye. The injection should be followed by the introduction of physiological salt solution to wash out the vein, thereby reducing the possibility of venous thrombosis. *Too much emphasis cannot be placed upon the necessity of using absolutely clean glassware and freshly distilled water of known purity in the preparation of any solution to be injected intravenously. Extreme care should be used in washing the medicine glasses, syringes, etc., free of lysol or other antiseptics which may drain into them from the sterile instrument used in handling them.*

All of the data in the preceding paragraph, concerning phenoltetraiodophthalein, can be applied to the preparation of the solution of tetraiodophenolphthalein with the following exceptions: The dose of tetraiodophenolphthalein is 3 to 3.5 gm. and is dissolved in 40 cc., or more, of freshly distilled water. Although practically all authors employing the intravenous method for cholecystography give it in one dose, we feel that the introduction of tetraiodophenolphthalein in two doses about one-half hour apart tends to reduce the possibility of reaction.

As time progresses, we find that there are fewer and fewer orders which are necessary for the patient. We still adhere strictly to the rule, however, of omitting breakfast on the morning of injection, and of confining lunch to a carbohydrate liquid intake. Better shadows of the gall bladder will be obtained if lunch is omitted entirely. On theoretical grounds, alkalization of the stomach with administration of 2 to 2.5 gm. of sodium bicarbonate every few hours, would aid in the production of the shadow (W. H. Cole). After every injection, we request the patient to remain in a reclining position for at least one-half hour. We feel that this is a very important factor in the prevention of reactions.

If observations on the reaction of the gall bladder to a fat meal are desired, we inject the solution in the evening at 8 or 9 P.M. and give the fat meal at 10 A.M. the next day, immediately after the first roentgenogram is taken.

The only disadvantage of phenoltetraiodophthalein over tetraiodophenolphthalein is its price. It is very possible that that obstacle may soon be overcome. In practically all other features, phenoltetraiodophthalien has advantages over its isomer in the intravenous administration for cholecystography.

**Oral Administration.**—Phenoltetraiodophthalein presents no advantages over tetraiodophenolphthalein in the oral method of cholecystography and therefore is not used in that capacity.



The first report of oral administration for production of cholecystograms was made by Menees and Robinson.<sup>1</sup> Their first work was done with sodium tetrabromphenolphthalein.

We favor the intravenous method of administration, but resort to the oral method with tetraiodophenolphthalein when veins are not accessible or when, through emotional reasons, a patient strongly requests the oral route.

The difficulty of incomplete dissolution of the tetraiodophenolphthalein in the capsules or pills, which was a serious drawback for some time, has efficiently been eradicated by Larimore.<sup>2</sup> He advocates giving the substance in gelatine capsules (with or without a thick coating of phenyl salicylate) containing 0.8 gm. (12 gr.) tetraiodophenolphthalein, 0.1 gm. (1.5 gr.) powdered agar, and 0.1 gm. (1.5 gr.) sodium bicarbonate. The above ingredients are of course thoroughly mixed in that proportion, before filling the capsules.

When using the oral method of administration we give 4 to 5 gm. (in 5 to 6 capsules), prepared as mentioned in the preceding paragraph, in the evening, about 9 P.M., with water, a few hours after the evening meal, which should be light and contain only small amounts of fats and proteins. If desired, the ingestion of the capsules can be extended over a period of one-half hour. The patient should go to bed after taking all capsules and lie on his right side for an hour or so following the ingestion, thereby aiding in the passage of the capsules through the pylorus before dissolution has taken place. No food is allowed until a roentgenogram of the gall bladder is made in the morning at about 9 A.M. A fat meal is frequently given a few minutes later. If the fat meal is not given, the patient's lunch should be restricted to carbohydrate liquid, to allow roentgenological observation at 1 P.M. and 5 P.M. These factors are discussed elsewhere in this chapter.

The powdered agar in the capsule presumably swells after becoming moistened with the intestinal juices, and breaks the contents of the capsule into fragments. The alkali contained therein prevents the formation of the acid tetraiodophenolphthalein, which is insoluble.

**Modifications of Administration.**—Since the advent of cholecystography there have been innumerable modifications offered, including

<sup>1</sup> Menees, T. O. and Robinson, H. C.: Oral Administration of Sodium Tetrabromphenolphthalein: Preliminary Report, *Am. Jour. Rentgenol.*, 1925, **13**, 368.

<sup>2</sup> Larimore, J. W.: Cholecystography: Oral Method of Administration of Sodium Tetraiodophenolphthalein, *Radiology*, 1926, **6**, 156.

the administration of the substance by the intravenous, oral, intraduodenal and rectal methods. Most of the authors, especially those using the intravenous and oral methods of administration, have reported entirely satisfactory results with the particular method which they describe. We feel that the explanation of conflicting ideas regarding the most satisfactory method of administration lies largely in the fact that as an individual uses one method, he becomes more efficient in it, and will have more satisfactory results than with any other which he may casually use. We believe, however, that the report of satisfactory results with so many methods is a point in favor of cholecystography, and probably signifies that a more efficient method will be described and that a more satisfactory drug for administration may be found.

The problem of determining the advantages or disadvantages of the intravenous over the oral method is a difficult one. There can be no dispute over the fact that when the solution is given intravenously there is a known amount of substance to be excreted, and the possibility of failure of complete absorption which occasionally presents itself in the oral method is completely eradicated. Also, it has been found by most workers that the intravenous method has given more accurate results. See pages 295 and 296 for a more extensive discussion of this point. On the other hand, the oral method is much simpler and requires less time. Although many, including ourselves, claim that less reaction is obtained from the intravenous method, it is quite apparent, that, should any very severe reactions occur, they would probably be more likely to occur following the intravenous method. Considering these facts, the problem of choosing between the intravenous and oral methods resolves itself, largely, into a matter of individual opinion and applicability. Although in our hands the intravenous method has revealed more advantages than the oral, there are some who find the oral just as efficacious.

The demonstration of the ability of a fat meal to empty the gall bladder, which was worked out by Boyden<sup>1</sup> and applied clinically by Sosman, Whitaker and Edson,<sup>2</sup> has been in the opinion of many a very important factor in the diagnostic accuracy of cholecystography, by either the intravenous or oral method. Whitaker<sup>3</sup> in

<sup>1</sup> Boyden, E. A.: The Effect of Natural Foods on the Distention of the Gall Bladder; With a Note on the Change in Pattern of the Mucosa as it Passes from Distention to Collapse, *Anat. Rec.*, 1925, **30**, 333.

<sup>2</sup> Sosman, M. C., Whitaker, L. R. and Edson, P. J.: Clinical and Experimental Cholecystography, *Am. Jour. Roentgenol.*, 1925, **14**, 495.

<sup>3</sup> Whitaker, L. R.: Experiences with Cholecystography, *Jour. Am. Med. Assn.*, 1926, **84**, 239.

reporting both an intravenous and an oral series, feels that the intravenous method is slightly more accurate than the oral. He employs a dose of 0.04 gm. per kilogram of body weight, made into a 5 per cent solution with distilled water. This is filtered and autoclaved, and when ready for injection is diluted to a strength of 2 per cent with salt solution (0.9 per cent) in a gravity apparatus, and allowed to run slowly into the vein. He advocates giving the solution either at night or in the morning, but specifies that no food should be partaken six hours prior, or ten hours subsequent to the injection. By giving the injection at night, less fasting is inflicted upon the patient. Ten hours after the injection a roentgenogram is taken. If a shadow is present, Whitaker advised giving the patient

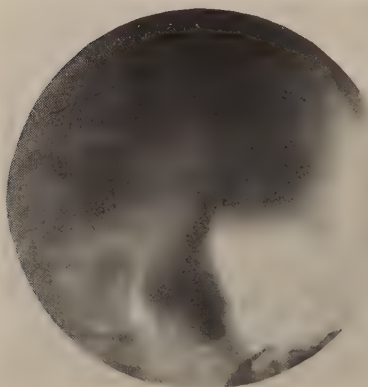


FIG. 106



FIG. 107

FIGS. 106 and 107.—Effect of fat meal. Fig. 106: Normal cholecystographic shadow after intravenous injection of phenoltetraiodophthalein. Fig. 107: The same individual one hour after the ingestion of  $\frac{1}{2}$  pint of cream and the yolks of 3 eggs.

a meal rich in fats, (including especially, butter, egg-yolk and cream) and following the meal by another roentgenogram in one hour. The amount and constituents of the fat meal as employed by different authors apparently varies considerably, but the one used by Boyden,<sup>1</sup> consisting of  $\frac{1}{2}$  pint of cream and the raw yolk of 5 eggs, appears most satisfactory. It contains the most important constituent (egg-yolk) and in an amount at least adequate. Case is not so particular about the kind and amount of fat in the meal employed in his series. (See following paragraph.) We have used a meal consisting of  $\frac{1}{2}$  pint of cream, 2 eggs and 1 piece of toast with 25 gm. of butter,

<sup>1</sup> Boyden, E. A.: Behavior of the Human Gall Bladder, *Anat. Rec.*, 1926, **33**, 201.

and have obtained adequate effect upon the gall bladder shadow. (Figs. 106 and 107.)

After experience with a large series of patients, Case,<sup>1</sup> who also favors the intravenous method, has developed a technique which is not only very efficient, but simple in procedure. He injects the solution intravenously in 100 cc. of Ringer's solution, by the gravity method, over a period of four or five minutes, at about 5 P.M. He states 10 to 12 patients can be injected in this manner within an hour's time. The patient limits himself to a carbohydrate evening meal and returns fifteen hours later for two films of the gall bladder, after which a fat meal is eaten. The meal used by Case is very similar to an ordinary breakfast—"The patient eating whatever is pleasing but including in the breakfast milk or cream and an egg-yolk." Case<sup>2</sup> feels that it is important to wait at least two and a half or three hours following the meal, before taking the second series of films. This completes the examination.

McCoy and R. S. Graham,<sup>3</sup> and Wilkie and Illingworth,<sup>4</sup> who prefer the intravenous method, make the injection between 8 and 10 P.M. The injection is made at that time apparently in the attempt to obtain an observation on the shadow of the gall bladder during the maximum density, which usually takes place between the tenth and fourteenth hour after intravenous injection of the dye. Postponing the time of injection in this manner, three or four hours after the evening meal, also allows a safer interval of time between ingestion of food and the injection of the dye.

Saralegui<sup>5</sup> has devised a special form of apparatus for the intravenous injection of the solution by the gravity method. Liest<sup>6</sup> suggests the idea of injecting the concentrated solution through the rubber tubing of a gravity set while physiological saline is being introduced.

Since the time when the oral administration of sodium tetrabromophenolphthalein was first reported by Menees and Robinson<sup>7</sup>

<sup>1</sup> Case, J. T.: The Relative Value of Cholecystography and the So-called Direct and Indirect Methods of Roentgenological Examination of the Gall Bladder, *Am. Jour. Roentgenol.*, 1926, **16**, 238.

<sup>2</sup> Case, J. T.: Personal communication.

<sup>3</sup> McCoy, C. C. and Graham, R. S.: Experience with Cholecystography in Cases Coming to Operation, *Jour. Am. Med. Assn.*, 1926, **86**, 1899.

<sup>4</sup> Wilkie, D. P. D. and Illingworth, C. F. W.: Cholecystography: A Report of Fifty-three Cases Controlled by Operation, *British Med. Jour.*, December 5, 1925, p. 1047.

<sup>5</sup> Saralegui, J. A.: Apparatus for Injection of the Stain for Cholecystography, *Semana méd.*, 1925, **2**, 308.

<sup>6</sup> Liest, L. J.: Technique for Intravenous Infusion of Sodium Tetraiodophenolphthalein in Cholecystography, *Radiology*, 1926, **6**, 300.

<sup>7</sup> Menees, T. O. and Robinson, H. C.: Oral Administration of Tetraiodophenolphthalein for Cholecystography, *Radiology*, 1926, **6**, 300.



numerous modifications, chiefly in regard to the coating of the pills or capsules, have been suggested. Menees and Robinson favor using a formaldehyde-treated capsule containing a thin paste made by adding olive oil to sodium tetraiodophenolphthalein. These are given during the evening meal, in a dose amounting to 50 mg. per kilogram of body weight.

The careful and painstaking work of Stewart<sup>1</sup> has done much to popularize the oral method. He advocates a mild cathartic the night before the preliminary examination, followed by a simple enema in the morning. At 6.30 P.M. (twenty-four hours after the cathartic) he suggests a meal limited to any of the following ingredients: Thick soup, creamed chicken, soft-boiled eggs, baked potatoes, milk, bread and butter. At 9.30 P.M. he advocates the ingestion of 2 capsules each containing 0.3 gm. (5 gr.) of tetraiodophenolphthalein, every fifteen minutes until 8 capsules have been taken. He favors a light coating of keratin. The patient reports at 9.30 A.M. and 1.30 P.M. for a film of the gall bladder. After the roentgenogram at 1.30 P.M., a fat meal is eaten and another film taken an hour after the meal.

Some interesting and well-controlled experiments have been conducted by Levyn and Aaron<sup>2</sup> comparing the relative values of different coatings of capsules with regard to their dissolution in gastric and duodenal contents. In most of their experiments they allowed the capsules containing sodium tetraiodophenolphthalein to remain in gastric juice for a period of two hours, after which time they were removed and placed in duodenal content. Their experiments included the use of: (1) Plain gelatin capsules; (2) double-walled capsules; (3) keratin-coated capsules; (4) formalin-treated capsules; (5) untreated double capsules, with the space between the large and small capsule filled with sodium bicarbonate. They found that the plain capsules digested readily, but that a large amount of the white acid form of tetraiodophenolphthalein, which was practically insoluble in the duodenal contents, was formed. The capsules which were treated with formaldehyde as well as those coated with keratin dissolved much more slowly, with the production of much less of the acid tetraiodophenolphthalein, but were inconsistent in the amount of dissolution of the sodium salt. The best results were obtained with the double capsules containing

<sup>1</sup> Stewart, W. H.: Some Interesting Observations on the Oral Method of Cholecystography, *Boston Med. and Surg. Jour.*, 1927, **196**, 509.

<sup>2</sup> Levyn, L. and Aaron, H. H.: Cholecystography by the Oral Method, *Radiology*, 1926, **6**, 204.

sodium bicarbonate in the space between the capsules. In this case, practically no insoluble acid tetraiodophenolphthalein was formed and a good dissolution in duodenal content was obtained. We have used capsules prepared in this way, with 0.25 gm. sodium tetraiodophenolphthalein in the smaller No. 3 capsule, and obtained very satisfactory results. Rarely will any of the contents of these capsules pass through the intestinal tract undissolved, as will be shown by a roentgenogram of the abdomen taken ten or twelve hours after the ingestion of the capsules.

The rectal and duodenal methods of administration were tried by us early in the development of cholecystography, but apparently were first reported by Weiss.<sup>1</sup> In our experience, solutions of halogenated phenolphthalein were poorly tolerated by the rectal mucosa, and the patient had difficulty in retaining the solution, regardless of whether it was introduced in diluted or concentrated form, or by the drop method. Stegemann<sup>2</sup> developed a method of injecting 6 gm. sodium tetrabromphenolphthalein in 200 cc. of water by preparing the rectal mucosa with opium suppositories. He found that suppositories of the dye were poorly tolerated. Palefski<sup>3</sup> and Stewart, Einhorn and Ryan<sup>4</sup> have also tried the duodenal method of administration. Stewart<sup>5</sup> has since apparently abandoned the duodenal method for the simpler oral method, which presumably is followed by less abdominal discomfort.

Pribram, Grünenberg and Strauss<sup>6</sup> have recommended the use of a preliminary injection of pituitrin in an attempt to empty the gall bladder first.

Sproull<sup>7</sup> has devised a method of oral administration of sodium tetraiodophenolphthalein without the use of capsules or pills. He permits the regular evening meal, and at 8 P.M. puts the contents of 4 or 6 capsules, each containing 0.5 gm. sodium tetraiodophenolphthalein, in cold cooked cream of wheat, mixes thoroughly and

<sup>1</sup> Weiss, Samuel: The Rectal and Duodenal Administration of Sodium Salt of Tetrabromphenolphthalein: A Preliminary Communication, *Am. Med.*, March, 1925, p. 161.

<sup>2</sup> Stegemann, H.: Cholecystography after Rectal Administration of Contrast Substances, *Münch. med. Wchnschr.*, 1926, **73**, 1281.

<sup>3</sup> Palefski, I. O.: Visualization of the Gall Bladder with Sodium Tetrabromphenolphthalein by Oral and Intraduodenal Administration through the Duodenal Tube, *Med. Jour. and Rec.*, 1925, **121**, 474.

<sup>4</sup> Stewart, W. H., Einhorn, M. and Ryan, E. J.: Recent Advance in Cholecystography, *New York State Jour. Med.*, 1925, **25**, 18.

<sup>5</sup> Stewart, W. H.: *Loc. cit.*

<sup>6</sup> Pribram, B. O., Grünenberg, K. and Strauss, D.: *Loc. cit.*

<sup>7</sup> Sproull, J. S.: Cholecystography: A New Method of Oral Administration of Sodium Tetraiodophenolphthalein without the Use of Capsules or Pills, *Am. Jour. Roentgenol.*, 1927, **17**, 316.

adds syrup to flavor. No other food is allowed until after a film of the gall bladder is taken at 8 A.M. By this method he finds less dye is left unabsorbed in the intestinal tract. A smaller dose is therefore needed and fewer reactions are obtained.

A recent modification suggested by Fantus<sup>1</sup> promises to offer a striking improvement in the oral administration. The simplicity of the oral method over the intravenous has been overbalanced by two disadvantages, namely, greater tendency toward reaction (especially nausea and vomiting) and lack of consistency in absorption. Fantus feels that he is able to eliminate, to a large degree, each of these disadvantages, by giving the tetraiodophenolphthalein in colloidal form. By passing carbon dioxide through a solution of tetraiodophenolphthalein until it is discolored, or by the addition of carbonated water, a fine precipitate is formed, which acts as a suspension. To stabilize this suspension he adds very dilute tragacanth mucilage. This colloidal mixture is white, is not offensive to taste, and according to Fantus, is sufficiently well borne by the stomach not to produce emesis. He finds 2 gm. tetraiodophenolphthalein sufficient when given by this method. The patient is advised to eat an early light supper and take the mixture just before retiring at 9 or 10 P.M. Frequent doses of sodium bicarbonate are advised. Two or three roentgenograms are taken the next day as desired. We have used tetraiodophenolphthalein in the colloidal form, on a few patients, as suggested by Fantus, and obtained shadows of the gall bladder without any reaction being experienced by the patient. The method is promising and deserves further trial.

In an endeavor to shorten the time required for the completion of a series of cholecystographic films, Spurling and Hartman<sup>2</sup> have employed the use of tolysin (ethyl ester of para methyl phenyleinchoinic acid) to aid in the rapidity of production of the shadow of the gall bladder. In their experiments they gave 1 gm. of tolysin by mouth at 7 A.M. and an intravenous injection of tetraiodophenolphthalein at 8 A.M. It was found that the lapse of time required for the production of shadows of maximum intensity could be greatly shortened in this manner. If the actual time required for the completion of a cholecystographic series could be consistently shortened, without jeopardizing the accuracy of diagnosis, it would be a great advantage.

<sup>1</sup> Fantus, B.: Peroral Administration of Colloidal Contrast Medium in Cholecystography, *Jour. Am. Med. Assn.*, 1927, **89**, 182.

<sup>2</sup> Spurling, R. G. and Hartman, E. E.: Choleretic Action of Tolysin (ethyl ester of para methyl phenyleinchoinic acid) in Cholecystography: Preliminary Report, *Jour. Pharmacol. and Exper. Ther.*, 1926, **30**, 185.

Great caution should be exercised in the use of tolysin for this purpose until it can be positively established that it is free from danger.

Since the development of cholecystography, Sabatini and Milani<sup>1</sup> have developed a technic for producing shadows of the gall bladder by the roentgen-ray, after the oral administration of large doses of sodium and strontium bromide. They advise using 10 to 20 gm., and fasting the patient over a long period of time. We were unable to produce satisfactory shadows of the gall bladder by using this method, although shadows were obtained. The patients also objected strenuously to the long fast and to the discomforts following such a large dose of bromides. McCoy and Graham<sup>2</sup> likewise did not find the method satisfactory.

In an endeavor to eliminate the occasional gastric disturbance which he obtained following oral administration of sodium tetraiodophenolphthalein, Pribram<sup>3</sup> introduced a new drug, diiodocincophen (di-iodo-atophan), which at first appeared to be superior to any other drug used for this purpose. Einhorn, Stewart and Ryan<sup>4</sup> report successful application of the use of diiodoatophan in a series of 14 cases. Nine of these were given diiodoatophan by mouth and 4 by the duodenal tube. In only 1 case was there any suggestion of reaction. This patient had only slight nausea. Pribram found, however, that a dose of about double the authorized 5 gm., would in many patients produce icterus.

It has been reported unofficially that after diiodoatophan had been put to more extensive use many toxic reactions, including severe jaundice were encountered, and the use of the drug was abandoned.

Recently Kirklin and Kendall<sup>5</sup> have introduced a new compound, diiododiethylether of disalicylphthalein, for oral use in cholecystography. They make an aqueous 10 per cent solution of the sodium salt which the patient drinks after an evening meal, free from fats. The dose employed is 8 to 10 gm. They report satisfactory cholecystograms after administration of the drug and they observed no toxic reactions in the patients, except a diarrhea in a few instances. Since the drug contains only two iodine atoms, and the tetraiodo compounds contain four, it is obvious that the dose would have

<sup>1</sup> Sabatini, G. and Milani, E.: Radiologic Visibility of the Gall Bladder after Administration of Alkaline Bromides by Mouth, *Internat. Med. Digest*, 1925, **7**, 259.

<sup>2</sup> McCoy, C. C. and Graham, R. S.: *Loc. cit.*

<sup>3</sup> Pribram, B. O.: Ueber ein neues Kontrastmittel zur röntgenologischen Darstellung der Gallenblase (di-iodocincophen), *Duetsch. med. Wchnschr.*, 1926, **52**, 1291.

<sup>4</sup> Einhorn, Max, Stewart, W. H. and Ryan, E. J.: Experiments with Biloptin (diiodoatophan), *Med. Jour. and Rec.*, 1927, **125**, 457.

<sup>5</sup> Kirklin, B. R. and Kendall, E. C.: A New Iodine Compound for Cholecystography, *Radiology*, 1927, **9**, 205.



to be much larger (almost twice) to obtain as much available iodine.

**Reactions.**—During the earlier period of development of cholecystography, before the use of tetraiodophenolphthalein, and especially phenoltetraiodophthalein, reactions were frequent and occasionally of an alarming nature. Now, however, we do not see any significant inconvenience to the patient due to reactions, and never do we see a reaction of serious consequence. As previously stated, the comparative toxicities of tetraiodophenolphthalein and phenoltetraiodophthalein are equal, but the smaller dose allowed by the latter, results in less reaction than that following the injection of tetraiodophenolphthalein. The following table illustrates the comparative reactions:

REACTIONS IN LAST 300 CASES OF TETRAIODOPHENOLPHTHALEIN.	
<i>Intravenous Method:</i>	
Total number of cases . . . . .	205
No reaction . . . . .	96 cases (46.9 per cent)
1st degree reaction . . . . .	75 cases (36.6 per cent)
2d degree reaction . . . . .	34 cases (16.5 per cent)
Total . . . . .	205
<i>Oral Method:</i>	
Total number of cases . . . . .	93
No reaction . . . . .	31 cases (33.3 per cent)
1st degree reaction . . . . .	17 cases (18.3 per cent)
2d degree reaction . . . . .	45 cases (48.7 per cent)
Total . . . . .	93
<i>Rectal Method:</i>	
Total number of cases . . . . .	2
No reaction except difficulty in retaining the solution.	
REACTIONS IN FIRST 489 CASES OF PHENOLTETRAIODOPHTHALEIN.	
<i>Intravenous Method:</i>	
Total number of cases . . . . .	481
No reaction . . . . .	297 cases (61.5 per cent)
1st degree reaction . . . . .	130 cases (27.3 per cent)
2d degree reaction . . . . .	54 cases (11.2 per cent)
Total . . . . .	481
<i>Oral Method:</i>	
Total number of cases . . . . .	6
No reaction . . . . .	3 cases (50.0 per cent)
1st degree reaction . . . . .	2 cases (33.3 per cent)
2d degree reaction . . . . .	1 case (16.6 per cent)
Total . . . . .	6

REACTION IN LAST 200 CASES OF PHENOLTETRAIODOPHTHALEIN.	
<i>Intravenous Method:</i>	
Total number of cases . . . . .	200
No reaction . . . . .	136 cases (68.0 per cent)
1st degree reaction . . . . .	51 cases (25.5 per cent)
2d degree reaction . . . . .	13 cases ( 6.5 per cent)
Total . . . . .	200

From the above tables it might appear that reactions following both the intravenous and oral method are still too frequent. Their seriousness is markedly diminished, however, since the reactions classified as first degree are practically insignificant. These reactions include only one of a group of symptoms consisting of vertigo, headache, backache, slight nausea, weakness and urticaria. All patients sustaining first-degree reactions were practically without exception, free from symptoms within a couple of hours following the injection. In the group classified as second-degree reactions are included: Severe nausea, vomiting, chill, circulatory depression, fever or severe abdominal cramps. If more than one of the symptoms occurring in first degree reaction were encountered, the reaction was classified as second degree. It is gratifying how rapidly patients recover from reactions. Rarely do even the most severe reactions persist over a few hours. We instruct the patients to observe themselves closely for the appearance of subjective symptoms, and there is no doubt that many of the complaints, especially in the "nervous" type of patient, are imaginary.

Two significant facts are discernible from the tables on the preceding page: (1) Fewer and less severe reactions were encountered after the intravenous injection of tetraiodophenolphthalein than after the oral administration; (2) fewer and less severe reactions were encountered after the use of phenoltetraiodophthalein than following the administration of tetraiodophenolphthalein. Furthermore, it can be seen that the number of reactions occurring during the use of phenoltetraiodophthalein has decreased as time has gone on, just as it did when using tetraiodophenolphthalein.

A great majority of authors who have used both the intravenous and oral methods extensively, and who find it convenient to use either method, are impressed with fewer reactions following the intravenous method, and with symptoms of shorter duration. In an article previously referred to, Case,<sup>1</sup> who tried both methods and has resorted almost entirely to the intravenous, calls attention to the fact that in his experience there were fewer reactions with the intravenous method of administration of sodium tetraiodophenolphthalein than with the oral. He states further that "only about 10 per cent of our patients suffer any unpleasant reactions, which they mention the next morning." He remarks that "reactions fall under three heads: (1) Those who have for any reason had the oral method instead of the intravenous; (2) those who have had injected tetrabromphenolphthalein or an iodine preparation which is not

<sup>1</sup> Case, J. T.: *Loc. cit.*

fresh; (3) certain individuals who racially are inclined to be of a neurotic disposition." In a personal communication he asserts that of over 1600 cases receiving injections for cholecystography, he had only 1 patient who gave him serious concern from the standpoint of reaction. To Case also belongs the credit of introducing the use of epinephrin, hypodermically, which he found so efficient in combating the reaction which sometimes accompanied injection of tetrabromphenolphthalein.

Whitaker,<sup>1</sup> who also has used both the oral and intravenous methods, reports that of 100 patients receiving tetraiodophenolphthalein orally, 68 had no reaction. Of the 32 sustaining reaction, 8 had nausea, 12 had nausea and vomiting, and 12 had diarrhea. In a series of 60 patients receiving the drug intravenously, 8 per cent had headache, nausea and vomiting. None of his patients, following administration by either method had any reaction of alarming nature. In a series of 20 patients receiving tetraiodophenolphthalein intravenously, Wheeler and Boyan,<sup>2</sup> who administered the drug in 2.5-gm. doses in 10 per cent solution followed by saline, had 1 case of "anaphylactic shock" but no other reactions. They state that this method is "less painful than pyelography." Camp, Reeves and Fields<sup>3</sup> report a slightly higher percentage of reaction in a series of oral than in intravenous cases, with about 31 per cent vomiting or severe nausea in each.

There has been considerable argument regarding the relation of the size of the dose to the frequency of reaction. It has occurred to us, and apparently also to Case<sup>4</sup> that there are other factors whose importance may be equal to the size of the dose. The reactions sustained in a series of intravenous cases reported by Wilkie and Illingworth<sup>5</sup> are so significant in this regard that we wish to submit them here in detail:

#### INTRAVENOUS INJECTION IN 14 PER CENT SOLUTION.

Number of patients receiving 5.5 gm. sodium tetraiodophenolphthalein	23
No reaction . . . . .	14 (61 per cent)
Nausea . . . . .	6 (26 per cent)
Nausea and vomiting . . . . .	2 ( 9 per cent)
Headache over night . . . . .	1 (4 per cent)
Number of patients receiving 4.12 gm. sodium tetraiodophenolphthalein	45
No reaction . . . . .	29 (64 per cent)
Nausea . . . . .	6 (13 per cent)
Nausea and vomiting . . . . .	9 (20 per cent)
Tingling over body . . . . .	1 ( 2 per cent)

<sup>1</sup> Whitaker, L. R.: Loc. cit.

<sup>2</sup> Wheeler, R. R. and Boyan, I. K.: Use of Sodium Tetraiodophenolphthalein in Cholecystography, Boston Med. and Surg. Jour., 1925, **193**, 676.

<sup>3</sup> Camp, J. D., Reeves, R. J. and Field, H.: Experiences with Cholecystography, Boston Med. and Surg. Jour., 1926, **194**, 976.

<sup>4</sup> Case, J. T.: Personal communication.

<sup>5</sup> Wilkie, D. P. D. and Illingworth, C. F. W.: Loc. cit.

It is very apparent in the above table that the patients receiving the larger dose of 5.5 gm. did not sustain a higher percentage of reaction than those receiving 4.125 gm. In fact, the difference shown, which is so slight that it should be called accidental, is in favor of the patients receiving the larger dose. In a later article, however, Wilkie and Illingworth<sup>1</sup> remark that since they have reduced the dose to 3 or 4 gm., the amount of reaction sustained by the patients has markedly diminished.

The difficulty in predicting the amount of reaction, by the patient's physical condition, suggests to us the possibility that individual idiosyncrasy to the drug is an important factor. We feel, however, that in many cases reactions have resulted from carelessness in injection, especially regarding the solvent, and cleanliness of glassware used in preparation of the solution. Racial characteristics may also be a factor. Case has remarked that there was a stronger tendency for the Semitic and Latin races to exhibit reactions than the other nationalities with which he had to deal.

However, the fact that there is a definite relation of size of the dose to reaction is borne out by a fatality following intravenous injection of 5.5 gm. of tetraiodophenolphthalein, reported by Huddy. Of the thousands of patients known to have undergone the test of cholecystography, this is the only authentic record of a fatality which has come to our attention. The dose of 5.5 gm. is much larger than that advised by us, and was not given in divided doses as we have advised. Up to the time of this fatality, it had been the custom of many European investigators to give large doses, but in view of results of equal efficiency obtained by a much smaller dose, it is reported that they are decreasing the dose to 3 to 3.5 gm.

It should also be emphasized that solutions should be freshly prepared, and not be accepted already prepared from the chemical houses.

Stewart,<sup>2</sup> who has been a strong advocate of the oral method, reports the following percentages of reactions:

*Keratin-coated capsules, 100 cases:*

Vomiting . . . . .	7 per cent
Diarrhea . . . . .	8 per cent
Nausea . . . . .	11 per cent
<hr/>	
Total . . . . .	26 per cent reaction

*Plain gelatin capsules, 100 cases:*

Vomiting . . . . .	12 per cent
Diarrhea . . . . .	12 per cent
Nausea . . . . .	15 per cent
<hr/>	
Total . . . . .	39 per cent reaction

<sup>1</sup> Wilkie, D. P. D. and Illingworth, C. F. W.: Cholecystography, British Med. Jour., April 2, 1927, p. 612.

<sup>2</sup> Stewart, W. H.: Some Interesting Observations on the Oral Method of Cholecystography, Boston Med. and Surg. Jour., 1927, **196**, 509.



He states that the difference noted above is not very significant, but that he prefers to have the capsules coated. None of the reactions were of severe nature.

Larimore<sup>1</sup> offered a valuable contribution to the explanation of reactions in oral cases in his report of 65 cases, 13 of which had alimentary reaction with diarrhea, and 5 of which had nausea and vomiting. All of the patients sustaining reactions had an achlorhydria. Incidentally a heavy shadow of the gall bladder was not observed in any of the patients with achlorhydria, although the dye apparently had been absorbed sufficiently.

Mather and Williams,<sup>2</sup> employing capsules with a triple coating of keratin in 125 cases, report low percentage of reaction, including 8 cases of nausea, 3 cases of vomiting (2 of which were immediate and probably due to emotional disturbance), and 2 cases of mild fever, which did not reach 100° F. They stress the importance of using a fresh preparation of the dye and not permitting the use of capsules which have been coated more than seven days previously.

Reactions obtained after the injection of halogenated phenolphthaleins may be classified either as constitutional or general, and local. The latter group consists almost entirely of inflammation about the vein caused by extravasation of solution outside the vein, and phlebitis. While we were using the concentrated solution of tetrabromphenolphthalein we obtained a slough (2 to 3 cm. in diameter) on the arms of two patients at the site of injection. These sloughs were superficial and were not disagreeable except that they healed slowly. Since the time when we began the use of solutions in a strength of 8 per cent or less, we have observed no instances of sloughing of tissue even though we have witnessed numerous occasions when extravasation was known to have occurred. The local reaction observed after extravasation of a few drops of solution with a strength no greater than 8 per cent consists of an induration and redness with moderate tenderness over the area of extravasation. We are convinced that the loss of a few drops of solution of this strength outside the vein will not produce a slough. The inflammation subsides rapidly under the application of hot wet packs.

The occurrence of phlebitis following intravenous injection is controlled largely by the care with which the injection is made. To prevent phlebitis we urge very strongly that the vein be washed

<sup>1</sup> Larimore, J. W.: *Loc. cit.*

<sup>2</sup> Mather, J. H. and Williams, W. R.: Cholecystography, *British Med. Jour.*, April 2, 1927, p. 614.

out with physiological saline after injection of the dye. This eliminates the possibility of stagnation of the hypertonic solution of the dye within the lumen of the vein. In 2 or 3 per cent of the patients under our care, who received intravenous injection of cholecystographic media, we obtained thrombophlebitis. In no instance was the outcome alarming. Tenderness and redness along the vein constitute the chief evidence of venous damage. On no occasion has there been any manifestation of extension into the axillary vein. The two most important procedures in the treatment of phlebitis of such origin is rest and application of hot wet packs. If the patient is ambulatory the forearm should be suspended in a sling. If the patient undergoes the examination in the hospital, the application of a wet towel and hot-water bag over the affected vein will serve as sufficient immobilization. Rarely does the inflammation fail to subside within a few days under this treatment. At no time have we been obliged to resort to any surgical procedures, such as incision of abscess, etc., to combat the complication of phlebitis.

A constitutional reaction may be obtained after either the intravenous or oral method of administration. As seen in the table on page 272, in the patients injected recently with phenoltetraiodophthalein, practically 70 per cent sustained no reaction whatever. The percentage of patients free from symptoms after the oral administration of tetraiodophenolphthalein is not so great. The type of reaction varies slightly, depending upon the method used. After the oral method the symptoms complained of in approximate order of their frequency are cramps in the abdomen, nausea, vomiting, diarrhea, and vertigo. Following the intravenous injection of phenoltetraiodophthalein or tetraiodophenolphthalein, the reactions are of a somewhat different type, vomiting and abdominal cramps being relatively infrequent. The symptoms complained of in order of frequency following intravenous injection of phenoltetraiodophthalein are slight nausea, vertigo, headache, weakness, urticaria and vomiting. We feel that resting in the prone position for one-half hour following intravenous injection is a strong factor in the prevention of any constitutional reaction. Of the few who were given tetraiodophenolphthalein orally several hours before retiring at night there also appeared a larger percentage of symptoms such as abdominal cramps and diarrhea.

The most alarming but also the most infrequent type of reaction is that which might be classified as circulatory shock. The rate of the heart beat is disturbed very little, but the blood-pressure is

found low. It is this type of reaction which responds so well to the hypodermic injection of 7 to 10 minims of adrenalin as first advocated by Case. Other stimulants including caffein, etc., may be administered but we have found the adrenalin adequate. Other symptoms, such as headache, nausea, malaise, etc., are treated symptomatically with aspirin, codein, etc. The abdominal cramps and diarrhea which are seen occasionally following oral administration of tetraiodophenolphthalein may be treated with paregoric or bismuth. The urticaria which is occasionally seen is readily controlled with adrenalin.

**Contraindications to Cholecystography.**—Although the intravenous method in our hands has been followed by slightly less reaction than the oral method, it seems reasonable to conclude that on account of the slower absorption, the oral method would have fewer contraindications if the patient's physical condition is very far below normal. Up to the present time, cardiac decompensation has been the only condition which has presented itself definitely as a contraindication. We have seen 1 or 2 cases of moderately severe circulatory shock after injection of patients having cardiac decompensation. Reid and Kenway,<sup>1</sup> however, have conducted detailed examinations of the heart following the injection of tetraiodophenolphthalein in human subjects, and were unable to detect any change in electrocardiograms or any other significant effect on the heart. We have injected patients, who were jaundiced because of cholangitis or common-duct obstruction, as well as patients with moderately severe liver damage due to other causes, (cirrhosis, carcinoma, etc.) without any greater percentage of reaction. Patients suffering from such illnesses, including also acute yellow atrophy of the liver, have been submitted to cholecystography by other observers without undue reaction. From a physiological standpoint, however, we feel that patients having acute liver infection or common-duct obstruction should not be submitted promiscuously to cholecystography. It has also been observed that patients with abnormally high or low blood-pressure are more susceptible to reaction than patients with blood-pressure near the normal limits. We feel also that threatened uremia is a contraindication to cholecystography.

<sup>1</sup> Reid, W. D. and Kenway, F. L.: The Action of Tetraiodophenolphthalein on the Heart, Jour. Am. Med. Assn., 1927, **88**, 540.

## SECTION V.

**THE RATIONALE OF CHOLECYSTOGRAPHIC INTERPRETATION.**

**Fundamental Considerations.**—When a hollow viscus is rendered visible by the roentgen-rays through increase of the opacity of its contents its characteristics are revealed as follows:

Location.

Relations.

Content.

Outline, or form.

Capacity, or size.

Capacity and outline are variable if the organ is distensible. If, in addition, such a viscus can modify the contained intensifying substance, then there exists in some degree a measure of both the nature of its contents and the modifying mechanism. The gall bladder is such a structure, and when studied cholecystographically in the normal subject the properties enumerated above can be satisfactorily observed. As the gall bladder effects changes in its contents a time factor of great import is thereby introduced. Furthermore, as the contrasting medium reaches the gall bladder by way of the circulation and through the excretory action of the liver, another time influence equally important is brought into play. Deviations in respect to the foregoing are the foundation of cholecystographic interpretation. It is essential, therefore, that a normal standard be established before interpretation of cholecystograms is undertaken.

As a basis for interpretation of cholecystograms, the beginner should have at hand those made on a normal subject. (Figs. 108 to 122.) These may be obtained by either the intravenous or alimentary administration of the dye, following the directions laid down in the section dealing with the choice of dyes and their administration. In the first method, there should be a beginning visualization of the gall bladder at about four, increasing density and alteration in size at eight, a maximum size at approximately twelve, and great diminution in size at twenty-four hours if the organ is seen at that time. Should the dye be given through the alimentary tract, visualization is first observed at about the twelfth hour thereafter. From that time onward the cycle of the cholecystographic phenomena is identical with that following the intravenous administration. The relative merits of the two methods of dye administration in their bearing on the interpretation of pathological cholecystograms will be discussed later.



**Location of the Gall Bladder.**—Anatomical teaching, which is based on an average of dissecting-room material, probably accounts for the erroneous general opinion that the position of the gall bladder is constant. The fact is that the visualized normal gall

FIG. 108

FIG. 109

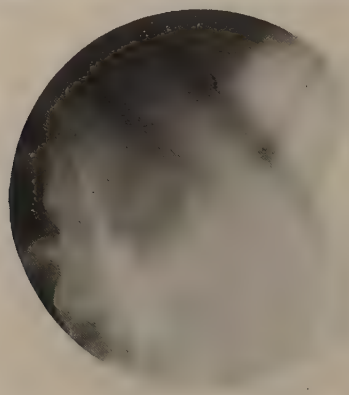
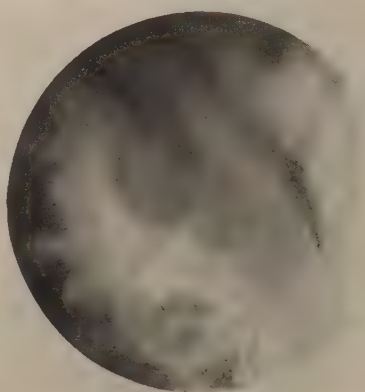
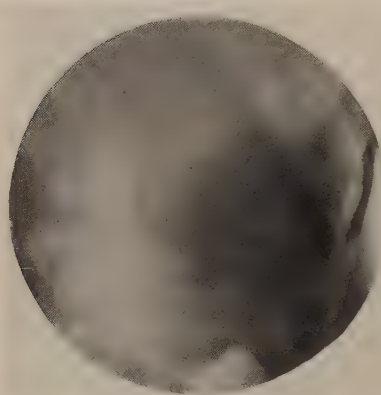


FIG. 110

FIGS. 108, 109 and 110.—Intravenous. Normal cholecystogram. Fig. 108: Gall bladder just visualized. Fig. 109: Increase in size and density. Fig. 110: Gall bladder faintly visualized.

bladder may be observed lying at any point from the level of the ninth rib posteriorly to the true pelvis in the vertical direction, and laterally from the right abdominal wall to the midline of the body. In *situs inversus* it will be found with its normal characteristics to the left of the midline. The question of position of the viscus has been

given exhaustive attention by Lange,<sup>1</sup> who points out that variability in this respect would account for many cases of gall stones overlooked in the past, because of the tendency to regard the position of the organ as of far greater constancy than is truly the case,

FIG. 111

FIG. 112

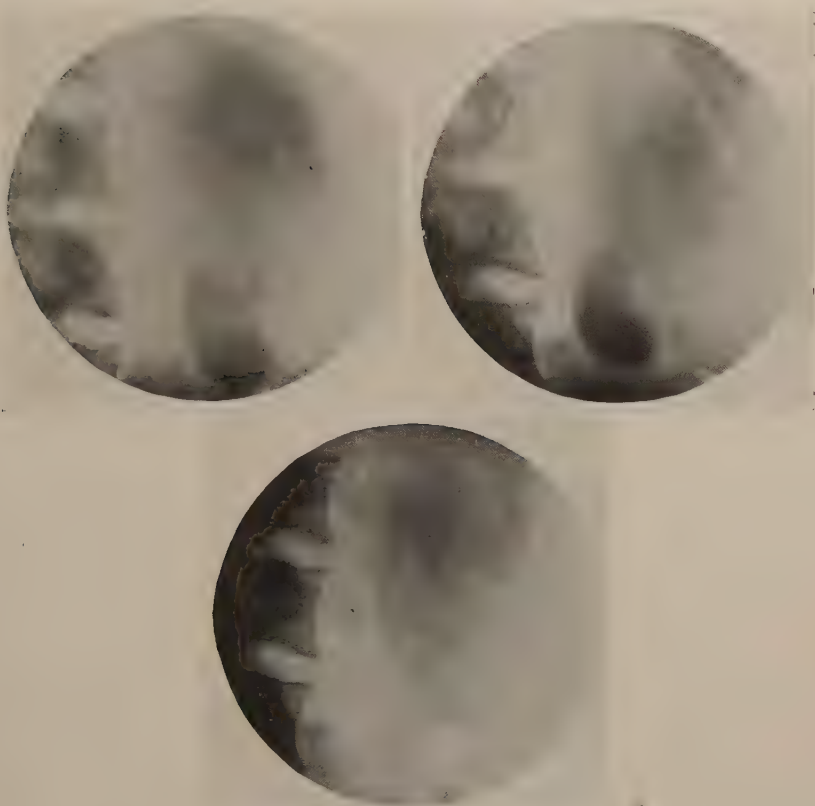


FIG. 113

FIGS. 111, 112 and 113.—Intravenous. Normal cholecystogram in a hyposthenic subject. Fig. 111: Gall bladder just becoming visualized. Fig. 112: Increased density through increased concentration. Fig. 113: Twenty-four hours; gall bladder not visualized.

the stones being missed through lying away from this accepted position, and either being in line with bones or out of the region examined. It should be borne in mind that the gall bladder is

<sup>1</sup> Lange: Gall Bladder as Revealed by Roentgen Ray, Jour. Am. Med. Assn., 1925, 85, 2021.

equally subject to those forces which affect the position of the other abdominal organs, posture, respiration, pressure of other structures, etc. The determining factor in the variability of position of the gall bladder is the particular physical make-up, or habitus, of the

FIG. 114

FIG. 115

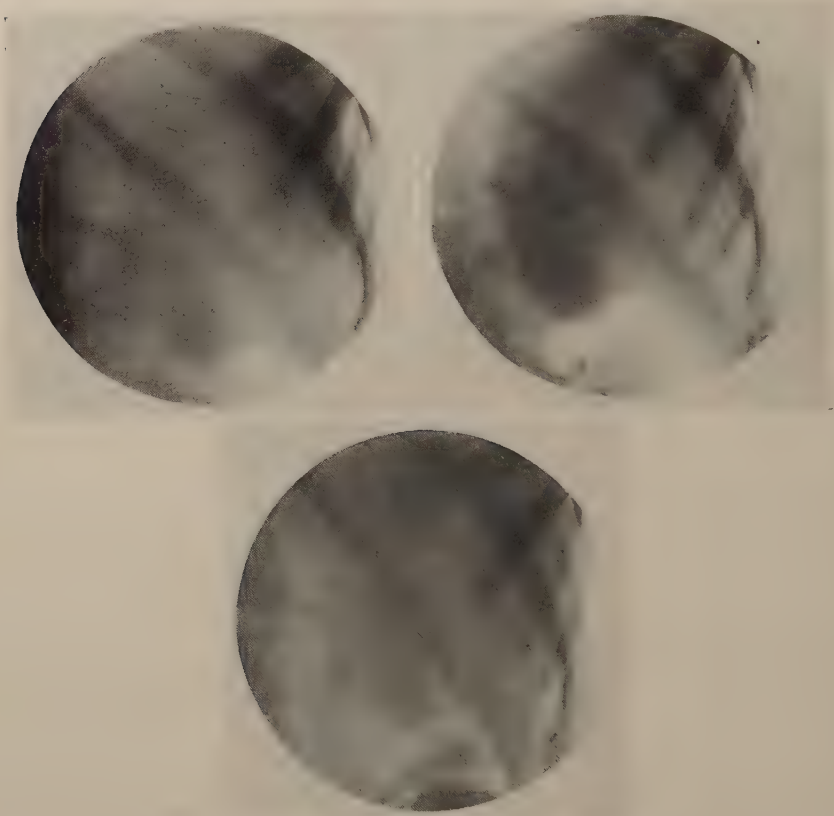


FIG. 116

Figs. 114, 115 and 116.—Intravenous. Same as Figs. 111, 112 and 113, in a sthenic individual.

individual. Consideration was first given to this by one of the writers,<sup>1</sup> who predicted that each type of habitus would exhibit a characteristic position, size and shape of the gall bladder, and that its tonus was likewise dependent on habitus. Tonus would play an

<sup>1</sup> Moore, S.: Cholecystography after the Method of Graham, Cole and Copher, *Am. Jour. Roent. and Rad. Therp.*, 1925, **13**, 515.

important part in governing the capacity, shape and emptying time of the vesicle. Observations on the visualized gall bladder have abundantly confirmed this view, and we now know that the observations of Mills<sup>1</sup> on the relation of bodily habitus to gastro-intestinal form and function apply with equal force to the gall bladder.

FIG. 117

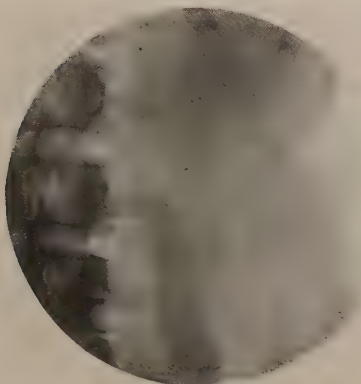


FIG. 118

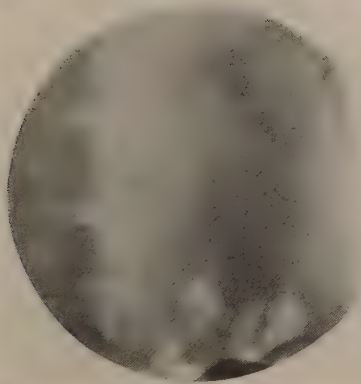


FIG. 119

FIGS. 117, 118 and 119.—Intravenous. Same as Figs. 114, 115 and 116, in an asthenic individual.

Davies<sup>2</sup> has recently published an elaborate study of the relation of the gall bladder shadow to bodily habitus. The test was carried

<sup>1</sup> Mills, R. W.: Relation of Bodily Habitus to Visceral Form, Position, Tonus and Motility, *Am. Jour. Roentgenol.*, 1917, 4, 155.

<sup>2</sup> Davies, Francis: Normal Cholecystography, *British Med. Jour.*, June 25, 1927.



out on 100 medical students by the oral method. Among other things, he concludes that the position of the gall bladder and its rate of emptying vary with the type of bodily habitus. He correlated bodily habitus, gastric motility and the rate of emptying the vesicle.

FIG. 120

FIG. 121



FIG. 122

FIGS. 120, 121 and 122.—Normal cholecystogram after oral administration of dye. Fig. 120: Fifteen hours after ingestion of dye. Fig. 121: Nineteen hours. Fig. 122: Twenty-three hours.

However, the latter is so greatly influenced by food intake and possibly by physical activity that it is doubtful if this theory as to emptying of the gall bladder can be actually substantiated. Davies' illustrations of the types of cholecystograms found in different types of habitus do not comport with our own views. Fig. 123 (suggested

by his article and modified from Mills) is a diagrammatic representation of our ideas of the position and form of the gall bladder as

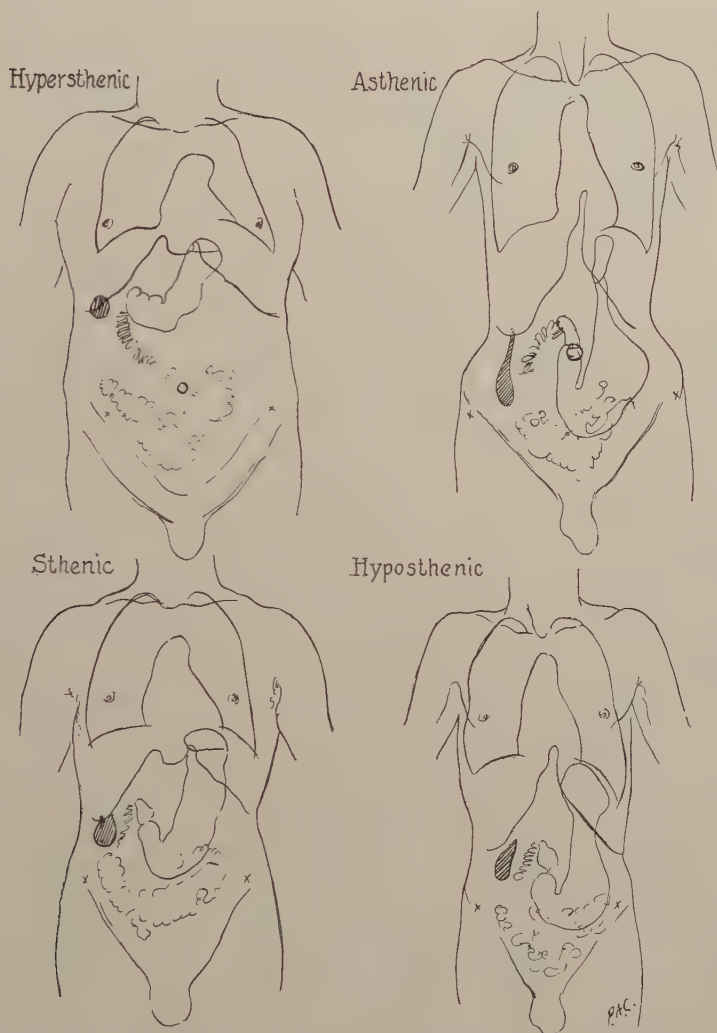


FIG. 123.—Diagrammatic representation of bodily habitus, form and position of stomach and gall bladder. (Modified from Mills and reproduced through the courtesy of the American Journal of Roentgenology and Radium Therapy.)

governed by the habitus of the individual. One of Davies' secondary conclusions is certainly open to discussion. He found considerable variation in the visualization of the gall bladder, which

is something that may always be expected with the oral administration of the dye. However, this article is the most comprehensive

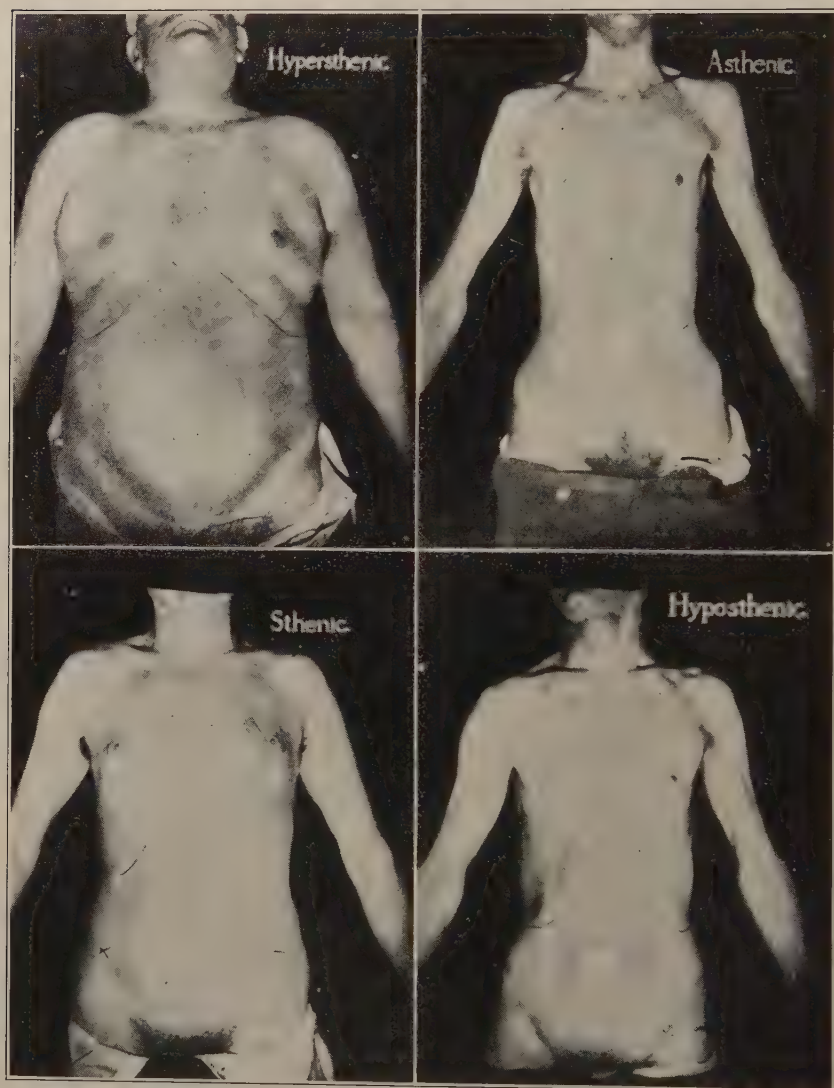


FIG. 124.—Photographs of types of bodily habitus. (After Mills. Reproduced through the courtesy of the American Journal of Roentgenology and Radium Therapy.)

study of normal individuals yet published, and is correspondingly valuable.

To clarify the matter of bodily types and their characteristic cholecystograms, the reader is referred to Figs. 124 to 128. From these it is seen that the heavy hypersthenic individual has a gall bladder in a high position and it usually lies horizontally, producing

FIG. 125

FIG. 126

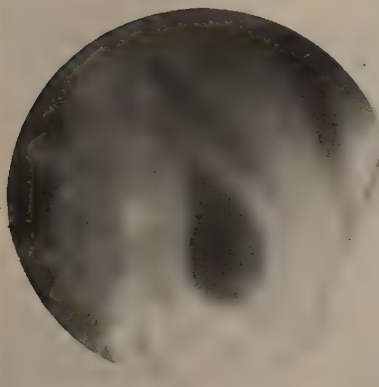
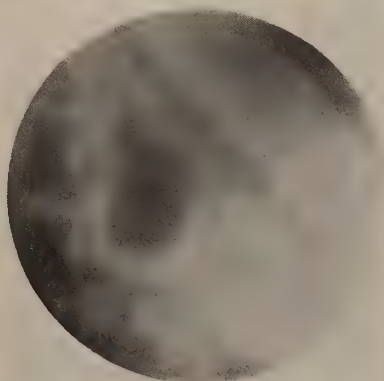
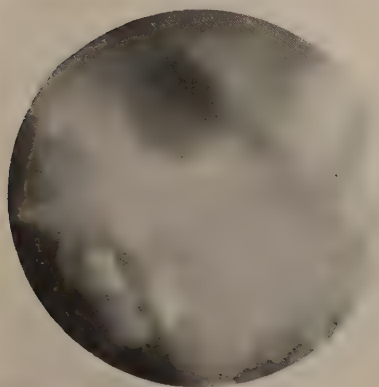


FIG. 127

FIG. 128

FIGS. 125, 126, 127 and 128.—Normal cholecystograms found in different types of bodily habitus. FIG. 125: Gall bladder of the hypersthenic type. Note circular outline. FIG. 126: Gall bladder of a sthenic individual. Note ovoid shape and lower position than in the preceding. FIG. 127: Hyposthenic individual. FIG. 128: Gall bladder of an asthenic. These are all extreme examples.

on the film a circular or oval shadow, chiefly of the fundus. At the other extreme, the asthenic will have a long narrow organ in a low position, and its body is brought into view. Intermediate types will be intermediate likewise as to the position, and hence the form,



of the organ. The influence of habitus on its size and form will be referred to again.

**Relations of the Gall Bladder.**—Location governs, to a large extent, the relations of the organ. When it is visualized, however, it must be borne in mind that its relations are in but two dimensions, unless lateral radiography or stereoscopy are employed. In the normal subject, relationship is established only to structures of a greater or lesser density; these are chiefly portions of the skeleton, the diaphragm as outlined by the base of the lung, and adventitious collections of gas in the gastro-intestinal tube. Relations of the gall bladder in abnormal conditions will be discussed in the interpretation of cholecystograms in differential diagnosis.

**Content.**—The estimation of this property is both quantitative and qualitative in nature. The former is an approximation rather than an exact determination, and as it plays an important part in fixing the outline and capacity of the vesicle, it will be given attention under these headings. The opaque gall bladder should be filled evenly and completely. Gross defects of filling indicate a pathological condition. In the present state of our knowledge, these are produced almost exclusively by calculi, although tumors, particularly papillomata, will also produce the same effect. Diffuse, hazy filling deficiency, with sedimentation of the dense bile in the fundus, is likely to belong in the category of the pathological gall bladder, except in the asthenic and when the film is made in the erect posture. Cholecystographic dyes are in solution in the bile, and hence the gall-bladder shadow should be homogeneous in density.

**Outline and Form.**—Habitus and tonus play an even greater part in the determination of outline and form than they do in position. There is also an intimate interdependence between form and outline and capacity of the organ. The gall bladder ranges from a circular, through various ovoid, to an elongated pyriform shape. When bisected in its long axis, the medial and lateral halves should be symmetrical, and there should be neither projection from, nor indentation of, its margins or fundus. A smooth indentation from either side and at the same level suggestive of a contraction of the muscularis, is a rare observation. It is referred to elsewhere and illustrated in Figs. 129 and 130. The size and shape of the visualized gall bladder are subject to an equal or almost greater degree of variation than its position, and may yet be entirely normal.

**Capacity, or Size.**—The true capacity of the gall bladder can only be estimated from cholecystograms, as they are two-dimensional. Excised gall bladders are far more constant in size than one would

gather from the study of their cholecystograms. The size of the latter is determined by the state of activity of the vesicle dependent on the digestive state, tonus and the mutual effects of habitus and position of the gall bladder in relation to the axis of the beam of rays employed in making the cholecystograms. It must be remembered that these represent the gall bladder in the "flat." Some idea of its third dimension, and therefore its capacity, may be gained by lateral and stereoscopic radiography. The true size of the gall bladder is never observed, because of distortion, the extent of this being dependent on the distance of the organ from the roentgen-ray tube and also from the film. Though the tube-film distance may be con-



FIG. 129



FIG. 130

FIGS. 129 and 130.—Modifications of outline of gall bladder, suggesting the existence of a peristaltic wave.

trolled, that between the gall bladder and film cannot. The normal gall bladder alters in size at the different hours of the cholecystographic examinations, as has been briefly outlined. Under starvation it is in a passive or "resting" stage as far as change of size is concerned. It probably rapidly attains its maximum, and the dye-laden bile is accommodated by the reduction in volume of the gall-bladder bile through the process of concentration. When food is given, decrease in size of the image is quickly apparent, especially if the food is fatty or contains egg-yolk. Since changes in size of the vesicle occur in the course of cholecystography, it is essential that the examinations be made at such periods as will register them. Capacity to alter in size is a measure of the elasticity

of the gall-bladder wall, and a knowledge of this quality is helpful in appraising the condition of the organ. (Figs. 131 and 132.)

**The Time Factors in Cholecystography.**—As in the case of variation in size, the rate of the appearance and disappearance of the gall-bladder image must be registered by examinations made at such periods that this may be accurately determined. This is of the utmost importance in reaching a conclusion as to the condition of the biliary tract in the pathological cases. The rate of filling and emptying of the vesicle in the normal individual is constant, except for the slight variation found in the different types of habitus, there being an increase in rate in the massive types and retardation in those of slighter make-up. (Figs. 133 to 136.) Periodic examina-

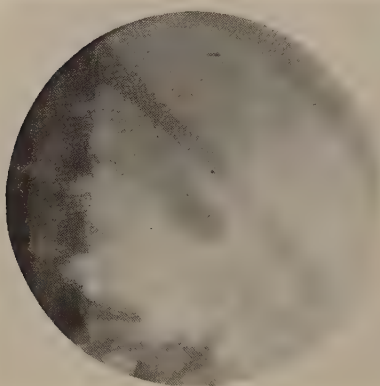


Fig. 131

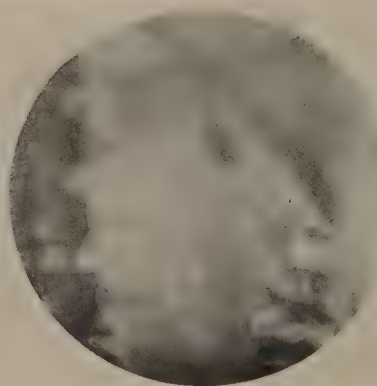


Fig. 132

Figs. 131 and 132.—Cholecystogram of normal individual, illustrating change in size and tonus. Intravenous injection of dye. Fig. 129: Four hours. Fig. 130: Eight hours, following food intake.

tions are absolutely necessary to the correct performance of cholecystography. One should never be content with a single film, no matter if it should appear to be normal in every respect.

**The Relation of Habitus and Tonus and Cholecystography.**—So many allusions have been made to habitus and tonus that, at the risk of being irrelevant, they will be discussed at this juncture. For further details as to the bearing of habitus on tonus the reader is referred to the writings of Mills,<sup>1</sup> Larimore<sup>2</sup> and Hurst.<sup>3</sup> As has

<sup>1</sup> Mills, R. W.: Relation of Bodily Habitus to Visceral Form, Position, Tonus and Motility, *Am. Jour. Roentgenol.*, 1917, **4**, 155.

<sup>2</sup> Larimore, J. W.: A Study of Blood-pressure in Relation to Types of Bodily Habitus, *Arch. Int. Med.*, 1923, **31**, 567.

<sup>3</sup> Hurst, A. F.: So-called Gastric Hypertonus and Gastroptosis and Atonic Dilatation of the Stomach, *British Jour. Radiol.*, April, 1927, **32**, 321.

been already stated, habitus determines to a large extent the position and, through this, the size of the image of the gall bladder. The tonus of the organ conforms to habitus, and to a material extent fixes its size and outline. In interpreting cholecystograms, there is

FIG. 133

FIG. 134

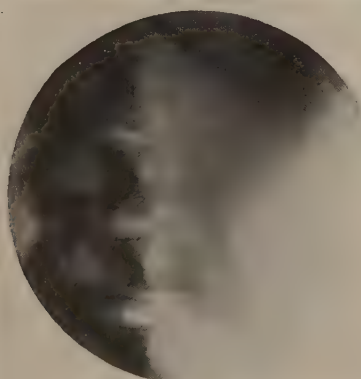
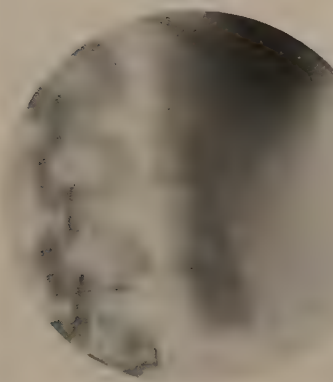
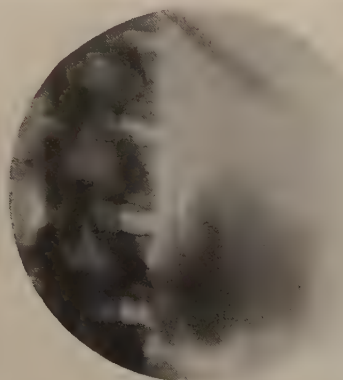


FIG. 135

FIG. 136

FIGS. 133, 134, 135 and 136.—Cholecystograms of asthenic. Illustrating general retardation found in this type of habitus. FIG. 133: Four hours. FIG. 134: Nine hours. FIG. 135: Twenty-four hours. FIG. 136: Thirty-two hours.

a well-marked tendency to ascribe pathological significance to those found in the extremes of body types, particularly in the asthenics. In the latter group are found the so-called "ptotic" and "atonic" gall bladders. It is widely believed and taught that "biliary stasis" is an etiological factor in the production of lithiasis and cholecystitis.



If we correctly understand the application of this phrase, it is restricted to the vesicle, and not the ducts. There has been some disposition to attach importance to the "atonic" and "ptotic" gall bladders in the production of stasis, by Chiray, Pavel and Milochevitch,<sup>1</sup> and Schöndube,<sup>2</sup> among others. These types of gall bladder are considered together, as we believe them to be practically identical and found under similar conditions. Atonicity of the vesicle, when observed, must be the local manifestation of the general muscular tonus. If this is low there is an accompanying retardation of the entire cycle of filling, concentration and emptying of the gall bladder, just as there is slowing of the progress of the opaque meal in the alimentary tract. If the gall bladder is clearly

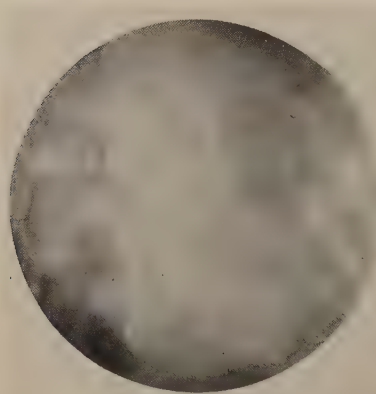


FIG. 137

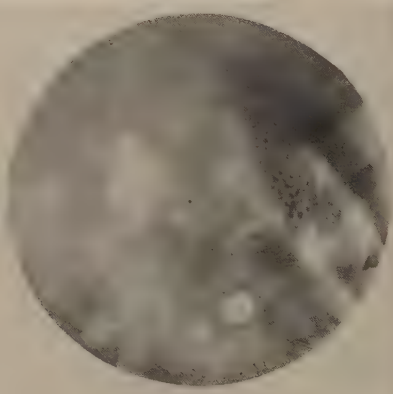


FIG. 138

FIGS. 137 and 138.—Case of lithiasis, showing evidence of change of tonus in gall bladder. Fig. 137: Phase of relaxation. Fig. 138: Tonic phase.

visualized there is no reason to suppose that its function is impaired and one must distinguish between "atonicity" and impaired function. "Ptosis" of the gall bladder could never be anything but evidence, in respect to that organ, of the general condition of the contents of the abdominal cavity, and if normally visualized, it is of no more significance than another ptotic viscus which is free from organic disease. Furthermore, and in its last analysis, this is but a matter of the asthenic habitus.

Allusion to gall-bladder tonus as observed cholecystographically

<sup>1</sup> Chiray, Pavel and Milochevitch: *Cholécystatonie: Etats hypotoniques et atoniques de la vésicule biliaire*, Presse méd., 12 septembre, 1925.

<sup>2</sup> Schöndube, William: *Klinische Erfahrungen zur Cholecystographie*, Münch. med. Wehnschr., 1926, 73, 1619.

necessitates reference to its filling and emptying mechanism. This is discussed in the chapter on physiology. There are two theories as to the manner in which the vesicle evacuates its contents: the active, by intrinsic muscular contractions, and passive, by resiliency, changes in tonus, etc. Our observations on the visualized organ, among other things, lead us to believe that intrinsic muscular contractions play only a partial rôle at most. Variations in gall-bladder size which might be attributed to variation of tonus are frequently noted in the course of cholecystography. A cholecystogram at its greatest size gives a distinct impression of atonicity; when it becomes smaller the reverse is true. These observations are best made following the administration of the fat meal. Such alterations coupled with an occasional finding of suggestive change in outline such as is seen in Figs. 131 and 132 constitute the cholecystographic evidence of the contractile mechanism of gall-bladder evacuation. In suitable cases of lithiasis identical changes of tonus can be demonstrated as in Figs. 137 and 138. As far as the radiographic evidence goes, it indicates that the burden of proof of the existence of emptying by intrinsic muscular contractions alone rests on its proponents.

It is only in the asthenic and related types that pathological import is ascribed to cholecystograms because of low position, the suggestion of lack of muscular tone of the gall bladder, and slight persistence of the shadows. In the hypersthenic group, the "better types" of Davies,<sup>1</sup> high position, relatively small size of the organ, and a more rapid filling and emptying, have so far received no attention as possible sources of cholecystic disease. And yet this is the group in which cholecystitis and cholelithiasis are most likely to occur, if it is true that fat persons exhibit a far higher incidence of biliary tract disease than others. Asthenics rarely become obese, so that they would hardly fall into that classification. There are no statistics on the incidence of biliary tract disease in the two major types of constitution. If biliary stasis is a feature of the low position of the gall bladder of the asthenic, and is an etiological factor in the production of cholecystitis or cholelithiasis, then the higher incidence of these two pathological conditions should be in the "poorer types," which is not the case. It is widely believed that the incidence of peptic ulcer is higher in the sthenic and hypersthenic types than in those of slighter physique. This led the writers to believe that a curve of the incidence of peptic ulcer plotted against the incidence of the various types of habitus would throw more light on

<sup>1</sup> Davies, Francis: *Normal Cholecystography*, *British Med. Jour.*, June 25, 1927.

this belief. It also led to combining in the curve the incidence of cholecystitis. This is illustrated in Fig. 139. The incidence of the types of bodily habitus is taken from Mills, and was gathered from 1000 consecutive examinations. The peptic ulcers number 106, operatively confirmed, and classified according to Mills' method. The curve for cholecystic disease is based on 136 operatively confirmed cases of cholecystitis where the type of habitus had been established. It is realized that the number of operative cases

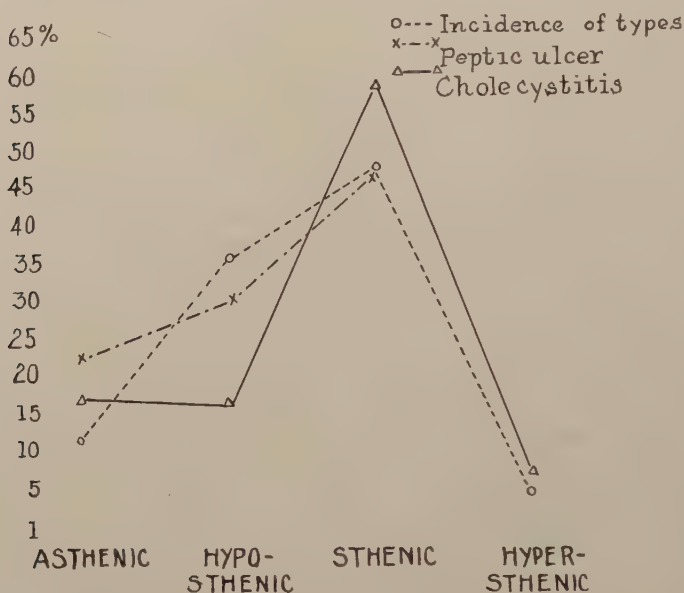


FIG. 139.—Curves showing the incidence of peptic ulcer and of cholecystitis in individuals of different physical types. The great preponderance of incidence of cholecystitis in the sthenic types is apparent. It is also observed that those of the asthenic type, which includes those individuals with visceroptosis, in whom incidence of biliary stasis is frequent, show a very low percentage of cholecystitis. The curves are based on 106 cases of peptic ulcer and 136 cases of cholecystitis, with operative confirmation in all cases.

is too small to permit absolute conclusions, but they are most suggestive of a higher incidence of cholecystic disease in the "better type." High gall-bladder position, with its concomitants, might seem conducive to gall-tract affections. (Fig. 139.)

Should one encounter a gall-bladder image of one type in an individual of dissimilar type, the problem of interpretation would be hard to solve. We have not met this, except in a spurious form which has been referred to, the gall bladder folded up in a high

position. Non-visualization of the gall bladder would probably occur in a condition where a pathological process had brought, for instance, a hypersthenic's gall bladder into an asthenic's position or form.

The interpretation of normal cholecystograms may be summed up with the statement that there is a wide normal variation of the gall bladder when revealed by this means in regard to its location, situation, contents, outline and capacity. None of these constitute, of themselves, pathological indications if the organ is well visualized, shows a progressive intensification of the shadow, alteration in size, and disappearance of the image shortly after the termination of the starvation period.

## SECTION VI.

### INTERPRETATION OF CHOLECYSTOGRAMS IN ABNORMAL CONDITIONS.

**Discussion of Dye Administration and its Relation to Interpretation.**—The choice of method of dye administration will be discussed at this point, since it has an important bearing on the interpretation of cholecystograms.

Oral administration of the cholecystographic dyes is overwhelmingly preferred in the United States. A hitherto unmentioned factor in determining the choice of method of giving the dye is that it is often relegated entirely to the radiologist. Naturally, intravenous manipulations are likely to be outside the scope of his activities; he will therefore not favor a method requiring them. Objections to the intravenous method are also founded on the belief that it is dangerous, time-consuming and complicated. We can agree to none of these.

At the last meeting of the Royal Society of Medicine of Great Britain, Section on Electrotherapeutics, Finzi<sup>1</sup> was of the opinion that the majority of those present preferred the intravenous use of the dye. In the discussion on cholecystography, Brailsford<sup>2</sup> stated that at the Congress of German Radiologists held the preceding year, the weight of evidence was in favor of giving the dye by mouth,

<sup>1</sup> Finzi, N. A.: (Discussion) *Proc. Roy. Soc. Med.*, vol. 20, No. 8, p. 12.

<sup>2</sup> Brailsford, J. F.: (Discussion) *Section of Electro-therapeutics, Proc. Roy. Soc. Med.*, vol. 20, No. 8, p. 12.



and if the gall bladder was not observed, such a result should be checked by intravenous administration.

It is our belief that the intravenous is far preferable to the oral method of dye administration. In addition to the reasons already given for this belief, is the fact that cholecystography is, among other things, a quantitative test. If alimentary administration is resorted to, two important variables are introduced, the amount and *rate* of dye absorption, either of which may profoundly affect the outcome of the procedure. Up to the present time we have no means of ascertaining what these may be. Until such determination can be made, it would seem that the results after oral administration will always be open to doubt in those cases in which there is deficient visualization of the vesicle. In the opinion of many observers a single film of the entire abdomen will satisfy them that the dye has been absorbed from the intestinal canal. Of this there is considerable doubt. The entire dose of dye may, in our opinion, remain in the small intestine and be so diluted that one might be deceived as to its having been taken into the circulation. Of course, radiography of the abdomen will determine whether or not the capsules or other media in which the dye was given have been broken up. In our experience, dye in solution has never been observed in the small intestine following either the oral or intravenous administration, except occasionally in the duodenum of experimental animals, chiefly dogs. If ingested dye reaches the colon and has been there an unknown length of time, the same phenomenon occurs as in the gall bladder; that is, fluid is taken from the colonic contents and there results sufficient concentration of the dye that its presence is revealed by radiography.

The matter of the appearance of the dye in the intestine is one which appeals to the writer as having led to errors akin to the frequent one of allusion to the deposition or concentration of dye on the outer surface of gall stones *in situ*. (Camp,<sup>1</sup> Blaine,<sup>2</sup> Pfahler.<sup>3</sup>) We have had occasion to radiograph known cases of calculi for the purpose of determining this point. The results of such experiments and other observations gave us no reason to suppose that cholecystographic dyes are either deposited on, or concentrated by, gall stones.

<sup>1</sup> Camp, J. D., Reeves, R. J. and Field, Henry, Jr.: Experiences with Cholecystography, Boston Med. and Surg. Jour., vol. 194, No. 21, p. 976.

<sup>2</sup> Blaine, E. S.: Biliary Disease from X-ray Viewpoint, Surg. Clin. North America, 1926, 6, 1004.

<sup>3</sup> Pfahler, G. E. and Widman, B. P.: Cholecystography; Routine Procedure in Roentgen-ray Examination of Gastro-intestinal Tract, Atlantic Med. Jour., 1926, 30, 5.

In this connection we have heard that the intravenous method was objected to because it made the gall-bladder shadow too dense, thereby causing difficulty in estimating its functional capacity. A similar mistaken idea is the alleged increase of density of the liver brought about by the presence of the dye. All of the foregoing seem to be misconceptions founded on incomplete realization of the degree of dilution of the dye and a lack of understanding of those agencies which bring about its concentration wherever it may be found.

However questionable adequate intestinal dye absorption may be, Stewart,<sup>1</sup> the leading American exponent of its oral administration, believes it to be of equal value with the intravenous, even in the cases of non- or faint visualization, provided the examination is carried out correctly in all its details. His operative confirmations certainly sustain his contention.

Whatever one's views may be in regard to the relative value of the two means of dye administration, it must be conceded that great credit is due to Menees and Robinson<sup>2</sup> for introducing and popularizing the oral method. It is certainly true that this diagnostic means has thereby been applied to many cases in which it would perforce have been omitted had the intravenous application been the only one available.

### THE CHOLECYSTOGRAPHIC CRITERIA OF THE PATHOLOGICAL BILIARY TRACT.

These are, in the order of their importance, the following:

Non-visualization of the gall bladder.

Faint visualization of the gall bladder.

Delayed appearance of the gall-bladder shadow.

Deformity of gall bladder.

1. Congenital.

2. Acquired.

(a) Intrinsic.

(b) Extrinsic, pericholecystitis.

Cholelithiasis.

Persistence of the gall-bladder shadow.

Excessive size of gall bladder.

<sup>1</sup> Stewart, W. H. and Ryan, Eric J.: Reliability of Cholecystography by the Oral Method as Shown by an Analysis of One Hundred Consecutive Cases, *Am. Jour. Roentg. and Rad. Ther.*, 1926, vol. **16**, No. 3.

<sup>2</sup> Menees, T. O. and Robinson, H. C.: Oral Administration of Tetraiodophenolphthalein for Cholecystography, *Radiology*, 1925, **5**, 211.

**Non-visualization of the Gall Bladder.**—After intravenous administration of the dye, this is the surest and most frequent sign of the diseased vesicle, if it is certain that the patient has taken no food during the period of supposed fasting. It may, however, result from pathological states aside from those of the organ itself, and it may be found in at least one physiological condition, late pregnancy. Among the former are many conditions preventing dye excretion, or the dye-laden bile from reaching the gall bladder. These include diseases of the liver (which must be very extensive to bring about this result), and obstruction of the intra-hepatic duct system, the cystic and common ducts. An occluded cystic or hepatic duct requires no comment. Non-visualization from obstructive causes has been dealt with elsewhere (Moore<sup>1</sup>). In the few patients with so-called catarrhal jaundice who have been submitted to this procedure, the viscus was not visualized. We have found that the gall bladder usually cannot be visualized in cases with jaundice, irrespective of its cause. Our practice, which we believe to be correct, is to omit cholecystography in such cases, as it may prove to be wholly deceptive. However, the test is harmless within this class of cases.

Alexander and Bond<sup>2</sup> found that in patients with enlargement of the liver from any cause, there was a non-visualization of the gall bladder with cholecystography. The probabilities are that enlargement of the liver has, as a concomitant, changes in the gall bladder, such as edema, etc., which preclude satisfactory concentration of its contents. It is possible that kinking of the cystic duct, due to the enlarged liver, with resultant slow ingress of the dye into the gall bladder may partly account for this result, as was believed by these workers. It is noteworthy that in the cases studied by these investigators there was no retention found with the Rosenthal test of liver function.

Cholecystography has been applied to 22 cases of pregnancy. After the thirty-second week of gestation we succeeded in demonstrating the gall bladder on but 3 occasions. The great mechanical difficulty of successfully raying in pregnancy, even with the patient in the lateral position, may possibly explain the non-visualization, for it was in the smaller subjects that we found the gall bladder. It was in a high position in all patients. Up to the fourth month of gestation the gall bladder can be readily demonstrated. This work is to be reported elsewhere in detail.

<sup>1</sup> Moore, S.: The Development and Application of Cholecystography, *British Jour. Radiol.*, August, 1926.

<sup>2</sup> Alexander, H. L. and Bond, R. C.: Unpublished.

From the preceding, and because it has a bearing on what is to follow in regard to non-visualization of the gall bladder, it is proper at this juncture to point out that interpretations of cholecystograms are to be made in collaboration with the clinician, or the radiologist should be in possession of certain facts bearing on the case under examination. However, we are of the opinion that, in common with all other radiological interpretation, that of cholecystography should be made as far as possible objectively and without too much influence being brought to bear by clinical data. This does not mean that common sense is to be omitted in this or any other form of radiological interpretation.

In the chapter on Physiology it is seen how fluid is removed from the gall-bladder bile, thereby concentrating it. With the use of sodium phenoltetraiodophthalein or other suitable dye the organ is visualized or not, according to its state of health or disease. From this we can conclude that probably any process, local or general, which would affect the removal of fluid from the gall bladder (for instance, an edema of its wall or of the liver) would have its results on the outcome of the test. Perhaps it was this that prevented gall-bladder visualization in the cases of enlarged liver.

We have had a few examples of malignant disease in the right upper abdominal quadrant and independent of the biliary tract, with grossly intact gall bladders which were not visualized. In one of these there was a large tumor of the right kidney. The mere bulk of the growth would not, on a mechanical basis, that is, through compression of the vesicle or its ducts, account for the non-visualization, so possibly there was a lymphatic obstruction which produced the result. It is probable that in any acute abdominal disease in which the liver is either enlarged or edematous the sequential phenomena observed in cholecystography would be prevented, and extending the idea, perhaps general acute diseases might likewise influence the results.

A case of perforated duodenal ulcer has been reported in which cholecystography resulted in non-visualization of the gall bladder. Operation revealed it somewhat edematous, but it was not sufficiently pathological to require removal. Repetition of the test at a later date showed a normal function. Should the test be carried out in acute disease, either abdominal or general, one might be deceived as to the existence of cholecystitis through the fact that there was a transitory inflammation or at least edema of the wall of the organ, with a temporary loss of function, which would not eventuate in cholecystitis.



We have had no experience with attempting cholecystography in acute disease, either general or abdominal, and have no reason to suppose that it should be so employed. In common with all other roentgen-ray procedures we believe that this test should be omitted in acute abdominal cases, unless it is imperative to know the state of the gall bladder. Such a case would be rare. A fact which is not sufficiently understood by clinicians is that the manipulation necessary for any roentgen-ray procedure in acute abdominal disease is not wholly free from the possibilities of mischief. Furthermore, a patient combating a condition of this sort does have, to some degree, a further strain thrown on him through the presence of the dye in the circulation. Finally, the technical roentgen-ray difficulties, coupled with the few observations as to the behavior of the gall bladder in acute disease, lead one to believe that cholecystography would doubtless eventuate in non-visualization of the vesicle, or at least an unsatisfactory performance of the test. Both of these would be equally deceptive in estimating the condition of the gall bladder.

We have carried out cholecystography in several subacute cases of appendicitis. There was non-visualization of the gall bladder in almost every instance, and invariably the latter organ has been found diseased. This illustrates and confirms our views on one phase of the pathogenesis of cholecystitis.

From the foregoing it is clear that the gall bladder may not be visualized even after the intravenous injection of the dye in certain conditions in which there is no reason to suppose that the organ is actually the seat of disease. However, these usually are obvious and there is no ground for holding this behavior of the gall bladder as constituting a weakness of cholecystography. If dye is given through the alimentary tract and non-visualization results, our view is that conclusions should not be drawn as to disease of the gall bladder unless this is strongly supported by history, symptoms and clinical examination. A cause of non-visualization of the normal gall bladder has been attributed to an hypothetical incompetence of the sphincteric action at the distal end of the common bile-duct. As yet no facts have been discovered to support this theory. Congenital absence of the gall bladder is to be thought of in non-visualization. It is a rarity and would be difficult to establish except at autopsy.

**Faint Visualization of the Gall Bladder.**—This is but a degree of gall-bladder deficiency of which non-visualization is the complete expression. In consequence it stands next to the latter in frequency

of occurrence and pathological significance. Since it represents stages in the loss of the concentration function, it is correspondingly difficult to appraise, and it is in this group that mistakes in cholecystographic interpretation are chiefly found. Ability to gauge the density of the gall-bladder image can only be gained by experience and observation. This density should be measured, so to speak, in terms of that of the rest of the cholecystographic film. In that way, variations of roentgen-ray exposure or the effects of body thickness of patients may be eliminated in part. There is no absolute scale of cholecystographic opacity because of the numerous variables that have their effect. Newell<sup>1</sup> has attempted to establish a photometric scale for comparing gall-bladder densities. His method is ingenious, but does not seem practical.

Faint visualization of the gall bladder may arise from all the causes that produce non-visualization. It might also be brought about by partial obstruction of the cystic and hepatic ducts. It might be due to an impaired excretory capacity of the liver, which only could be certainly discovered by a test of liver function. Far more commonly it indicates a cholecystitis of lesser intensity than that observed in those cases in which non-visualization has resulted. With faint visualization of the vesicle there is nearly always some evidence of lack of distensibility or elasticity of its wall manifested by constancy in size, or only sluggish change. There is little or no variation in shadow density at the various periods of examination.

We attach great pathological importance to the faintly visualized gall bladder if the dye is given intravenously. On the other hand, we feel that this sign is to be ignored in oral administration, since there are so many factors, vomiting, diarrhea, insufficient dye absorption, non-solution of dye, etc., which vitiate the test.

**Delayed Appearance of the Gall-bladder Shadow.**—Late appearance of the image of the vesicle can be due to any parenchymatous condition of the liver which retards the excretion of the dye. It is possible, but unlikely, that the intrahepatic-duct system might be so affected that in the absence of true obstructive phenomena, egress of the dye-filled bile might be slowed. Eliminating these two possible causes, then late appearance of the gall-bladder image indicates a slow removal of those elements of the bile which are taken up through the concentrating function. This is the result of a pathological condition, as has been outlined before. (Figs. 140 to 145.) This finding is an unusual one and has been encountered on so few

<sup>1</sup> Newell, R. R.: Roentgenographic Estimation of Concentration of Tetraiodophenolphthalein in the Gall Bladder, *Am. Jour. Roent. and Rad. Ther.*, 1927, **17**, 443.

occasions (eight cases) that we lack definite ideas in regard to it. Should it be found after oral administration and an image of good density be secured, one would be justified in holding the gall bladder to be normal.

FIG. 140

FIG. 141

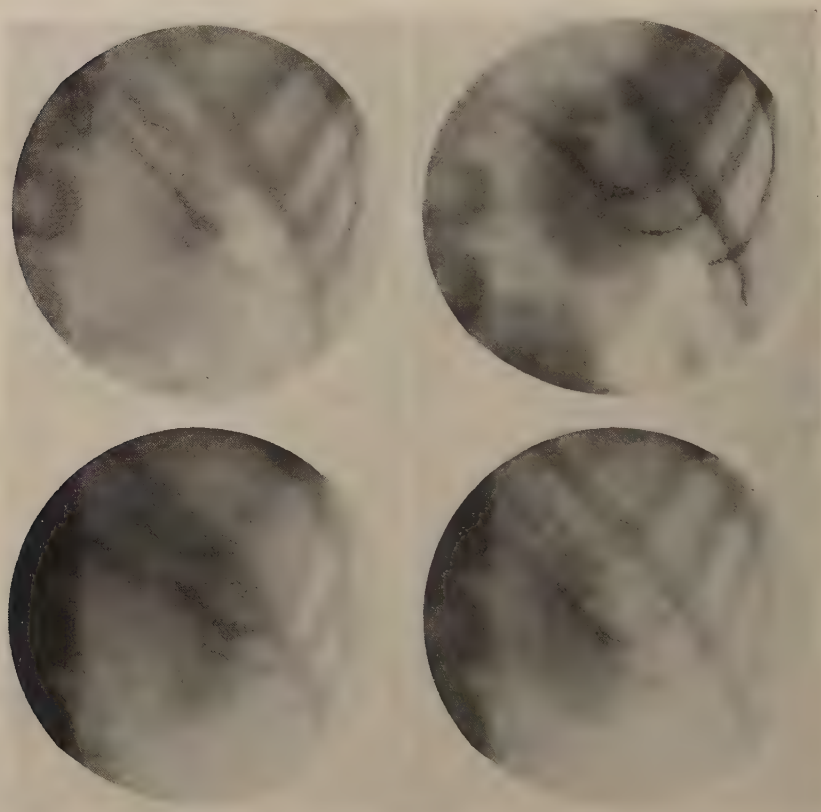


FIG. 142

FIG. 143

FIG. 140, 141, 142 and 143.—An example of delayed concentration of bile. Fig. 140: Four hours; gall bladder scarcely visualized. Fig. 141: Eight hours; visualization is clearer. Fig. 142: Twenty-four hours; visualization stationary. Fig. 143: Thirty-two hours; gall bladder at its greatest density.

**Deformity of the Gall Bladder.**—1. **Congenital.**—Though belonging properly in the normal classification, the congenital anomalies of the gall bladder and their cholecystograms will be dealt with here, for they are manifested chiefly by aberrations of form. This necessitates their differentiation from the deformed gall bladders of

acquired origin. Congenital absence of the organ and its part in *situs inversus* are referred to elsewhere. Duplication of the gall bladder is readily found by cholecystography, provided the organ is not too extensively diseased. Since the discovery of cholecystography it has been found preoperatively by several observers. (Fig. 146.) There are numerous variations in the course, position and relations of the neck of the gall bladder. Some of these are observed in cholecystograms, particularly tortuosity and apparent reduplication of the neck. This has even been a source of difficulty in interpretation. These variations are to be ignored in the face of normal cholecystographic behavior. Reference to the chapter on anatomy will make them clear, and the illustration found there will aid in the interpretation of puzzling cholecystograms.

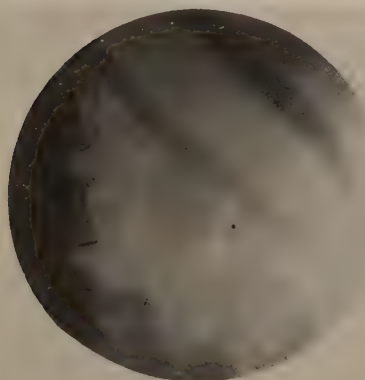


FIG. 144



FIG. 145

FIGS. 144 and 145.—Delayed appearance of gall-bladder image, with faintness of shadow. Non-visualization at four and eight hours after intravenous dye injection. Gall bladder observed at twenty-four and thirty-two hours.

2. **Acquired.**—It was some time subsequent to our taking up cholecystography that we were brought to a realization of the significance of acquired deformity of the gall-bladder image and attempted to distinguish between its true and pseudo forms. If the cholecystograms reveal a misshapen vesicle, unless it is constantly present and persists when rayed in such positions as will permit the organ to shift, one must be very wary in ascribing pathological significance to this finding. The same caution should guide one in regard to a bizarre location. The long mobile gall bladder of the asthenic when rayed with the patient in the prone posture may be readily folded on itself and dislocated in a most





FIG. 146.—An example of double gall bladder not found by cholecystography, but because of the two groups of stones observed in the radiograph. (Illustration kindly supplied by Dr. B. H. Nichols, of Cleveland, Ohio, and reproduced through the courtesy of Radiology.)

deceptive fashion and seem to be fixed. A mistake from this source nearly resulted in an operation on the vesicle in one of our earliest cholecystographies. (Fig. 147.) Unusual shapes and the suggestion of fixation, if persistent and especially if coupled with a certain faintness of shadow, indicate the possibility of an actual acquired deformity. This may be intrinsic or extrinsic in origin.

(a) *Intrinsic Deformity*.—A localized disease process in the wall of the organ may be followed by repair and fibrosis, which produces a permanent irregularity of outline with preservation of normal or nearly normal functional capacity. Attention was first called to this by Wilkie and Illingworth.<sup>1</sup> There is another deformity found in cholecystograms which is most infrequent and which seems to

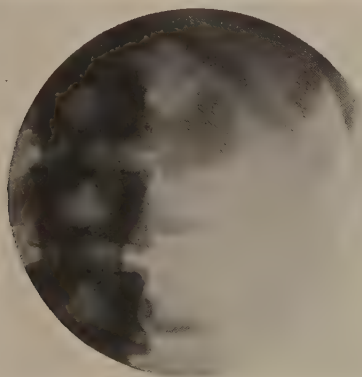


FIG. 147.—At operation for chronic appendicitis the gall bladder was found free and pendulous. The condition observed in the cholecystogram was obviously due to the organ being folded up on itself and not to adhesions.

differ from that described by those authors. In it there is present what may be termed an incisura which crosses the body of the vesicle, almost dividing it into two parts. (Figs. 148, 149 and 150.) In the absence of pathological specimens, one of us<sup>2</sup> has advanced the theory that this is comparable to peptic ulcer with its incisura, both as to its nature and origin. Localized deformity of the wall of the gall bladder in which the muscularis is involved and in which the organ is otherwise functionally intact most probably results from a local destruction of tissue which is slight in extent and sterile in

<sup>1</sup> Wilkie, D. P. D. and Illingworth, C. F. W.: Cholecystography: A Report of Fifty-three Cases Controlled by Operation, *British Med. Jour.*, December 5, 1925.

<sup>2</sup> Moore, S.: Further Observations on Cholecystography, *Med. Jour. and Rec.*, February 16, 1927.

nature. In the chapter on Diagnosis, syphilis of the gall bladder is discussed. In time, it will no doubt be discovered that some of these malformations of the gall bladder disclosed by cholecystography will be found to have originated from that disease. Deformi-

FIG. 148.

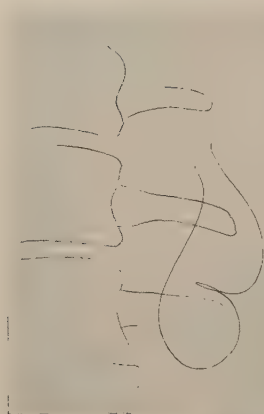


FIG. 149.

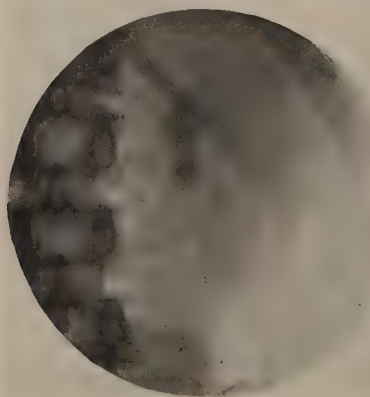
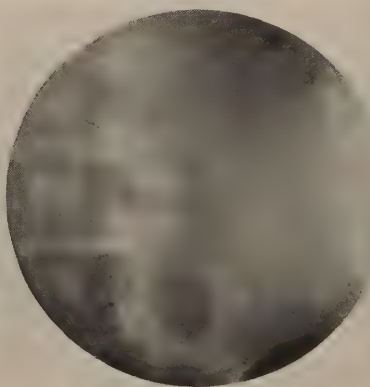


FIG. 150.

FIGS. 148, 149 and 150.—Fig. 149: Incisura crossing body of gall bladder. Fig. 148: Tracing of same. Fig. 150: A similar division of gall bladder, of indeterminate nature.

ties of the vesicle are much more commonly brought about by adhesions than by localized intramural disease.

(b) *Extrinsic Deformity*.—In Section II the origin of pericholecystic adhesions is described. According to our thesis regarding the visualized gall bladder, should it be inflamed sufficiently to

originate adhesions, permanent disappearance of the concentrating function would follow; consequently, it would never be visualized, unless the cholecystitis had healed with a restoration of its concentrating function, a possibility which may occur in a few cases but perhaps not in the great majority. Therefore, pericholecystic adhesions discovered cholecystographically must originate in the second class of possibilities outlined by Schürmayer.<sup>1</sup> It is a fact that a very large proportion of diseased gall bladders are found at operation to have extensive adhesions, particularly where there is cholecystographic non-visualization. The incidence of adhesions can be gathered from the figures quoted by Brailsford,<sup>2</sup> who writes that the Mayo Clinic reported them in 29.7 per cent of 1743 cases and that Pavoit and Tripier found the gall bladder adherent to the colon 75 times in 1000 operations. Though commonly found at operation, radiological demonstration of pericholecystic adhesion is rather unusual.

In order to determine the radiological incidence and nature of extrinsic gall-bladder deformity and fixation, the cholecystograms of 1218 patients were reexamined. An attempt to secure a precise application of these terms was unsuccessful; consequently "pericholecystitis" will include both of them. There is some advantage in this, since acquired extrinsic deformity has some degree of fixation as an accompaniment and, what is more to the point, fixation will produce it, the extent of the latter being determined by the duration of the former.

In the 1218 examinations there was no example of a misshapen gall bladder that one might consider of congenital origin. Persistent deformity of the organ assumed to be of acquired extrinsic origin was observed 36 times. (Figs. 151, 152, 153, 154 and 155.) In 25 cases the cholecystograms were less than, and in 11 they were normal in density. The latter group are either mistaken interpretations (the most probable explanation) or are examples of pericholecystitis in its incipency.

It seems to the writers to be safe to state that when pericholecystitis is discovered cholecystographically, it probably arose through disease of adjacent organs, although of course it may also represent a cholecystitis that is healed in the pathological sense. In spite of the fact that a gall bladder so involved must have a fairly

<sup>1</sup> Schürmayer, C. B.: Pathologische Fixation bzw. Lagveränderung bei Abdominalorganen und die röntgenologische Diagnosestellung, *Fortschr. auf. dem Gebiete der Röntgenstrahlen*, 1910, **15**, 308.

<sup>2</sup> Brailsford, J. F.: The X-ray Diagnosis of Pathological Conditions of the Gall Bladder, *British Jour. Radiol.*, 1927, **32**, 81 and 319.



good function (otherwise it could not be visualized), it seems best to class it as pathological. It is certainly true that in our material such cases have given symptoms which, though rather confusing,

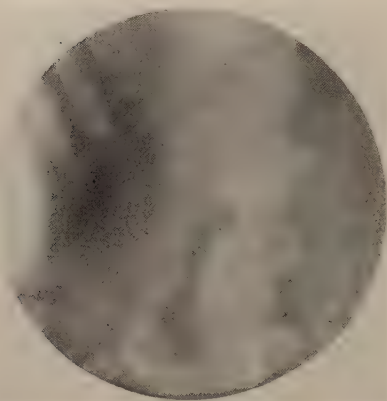


FIG. 151

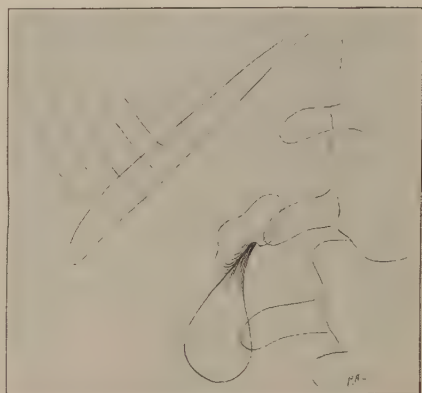


FIG. 152

FIGS. 151 and 152.—Example of pericholecystitis, with biloculation of the gall bladder and partial torsion of its lowest portion. Fig. 151: Cholecystogram, which is faint. Fig. 152: Tracing of same.



FIG. 153

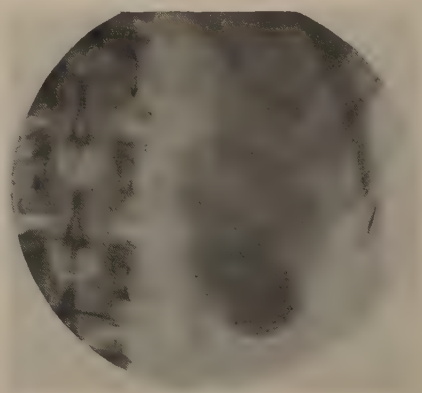


FIG. 154

FIGS. 153 and 154.—Pericholecystitis; gall bladder folded on itself and its fundus fixed. Fig. 153: Drawing made at operation. Fig. 154: Cholecystogram, approximately normal in density.

were undoubtedly present, and relief followed cholecystectomy. Furthermore, such an organ must have its capacity for change in size greatly interfered with and this must be a precursor of the loss of its remaining functions.

If, on laparotomy, the gall bladder should be found extensively adherent and the cholecystograms have indicated neither deficiency of concentration nor distortion of outline, it should be considered pathological and be dealt with accordingly. The study of pericholecystitis by cholecystography unquestionably confirms the observations of Schürmayer and later, in this country, by Pfahler.<sup>1</sup> In the study of gall-bladder deformity, if the organ is visualized after the dye is given orally, the interpretation is identical with that following intravenous administration.

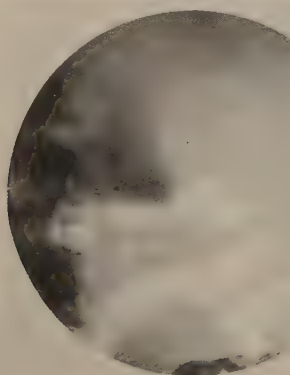


FIG. 155.—Cholecystogram in case of persistent deformity. Patient in erect posture. Dense gall-bladder shadow.

**Cholelithiasis.**—Before beginning the discussion of cholecystography in cholelithiasis, gall stones should be defined. In relation to radiography they are of but two varieties, the opaque and non-opaque. The former contain enough inorganic material, principally calcium, that they can absorb sufficient roentgen-rays to produce an image on radiography. They are sometimes called “positive,” “dense” or “calcium” stones. The non-opaque stones, as the term implies, are permeable to the roentgen-rays, and are composed almost wholly of organic material, chiefly cholesterol. They are

<sup>1</sup> Pfahler, George E.: Gastric and Duodenal Adhesions in the Gall-bladder Region and their Diagnosis by the Roentgen-rays, Jour. Am. Med. Assn., 1911, **56**, 1777.

visualized radiographically only when situated in a medium of greater or less density than themselves. They are known as "negative" or "pure cholesterol" calculi. Probably a goodly proportion of them contain calcium, but its determination would have to be

FIG. 156

FIG. 157

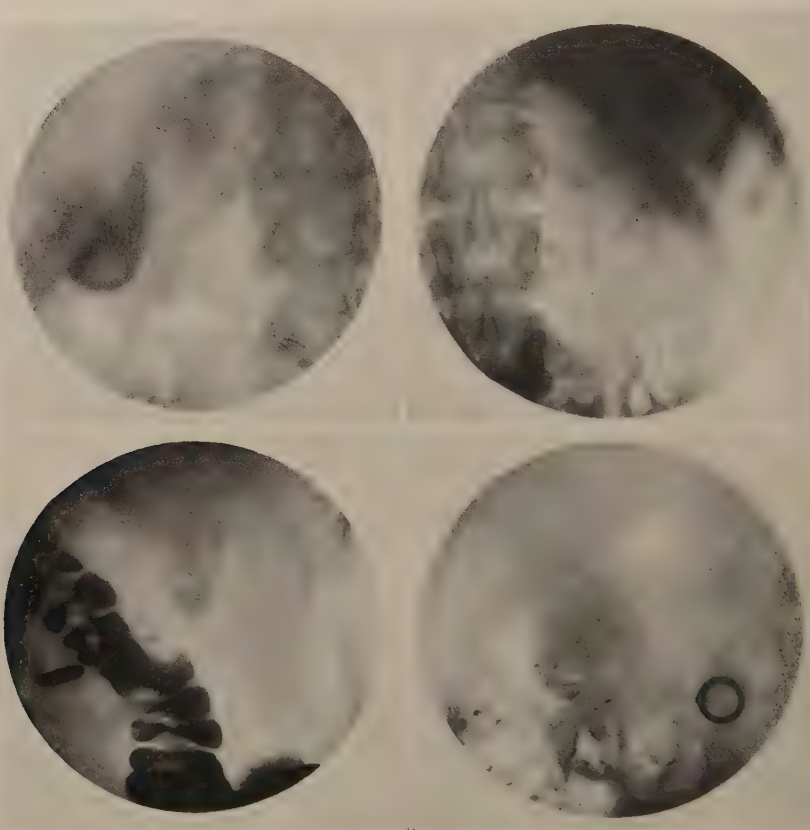


FIG. 158

FIG. 159

FIGS. 156, 157, 158 and 159.—Examples of non-opaque stones in gall bladder with approximately normal concentration. Fig. 156: Single large stone. Fig. 157: Two large non-opaque stones. Fig. 158: Multiple rather large non-opaque stones. Fig. 159: Small stones; an example of "mottled" cholecystogram.

made by chemical, not roentgen-ray, methods. Much confusion has arisen through the use of the terms "positive" and "negative" gall stones; therefore "opaque" and "non-opaque" will be employed.

On the institution of cholecystography, contrary to our expectations, the finding of gall stones proved quite disappointing. We had

hoped to enhance their density, thereby making them more readily discoverable, and anticipated visualizing many gall stones that had hitherto escaped detection. In retrospect our experience appears quite startling. In our material, in virtually all the cases of lithiasis in which the stones contained sufficient calcium for their demonstration by simple radiography, there was almost never any concentration of the dye in the gall bladder. Where stone and dye were both present there was no more intensification of the stone shadow than one would anticipate from the double density, as has been

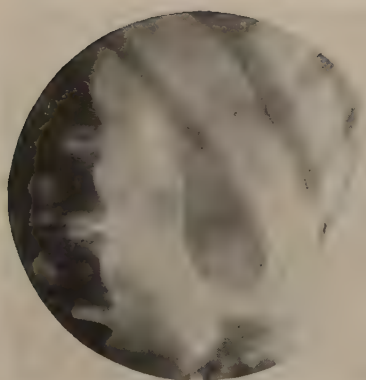


FIG. 160



FIG. 161

FIGS. 160 and 161.—Fig. 160: Cholecystogram of a large non-opaque stone. Fig. 161. Photograph of excised gall bladder and stone.

pointed out elsewhere.<sup>1</sup> On the other hand, a type of stone in a phase of gall-bladder disease which it was formerly impossible to discover short of opening the organ, is now frequently detected. There are the non-opaque stones found in the gall bladder which still has an intact absorptive function. (Figs. 156 to 163.) They appear as single or multiple dark-filling defects, usually circular, and with rather sharply defined margins. Their size ranges

<sup>1</sup> Moore, S.: Further Observations on Cholecystography, *Med. Jour. and Rec.*, February 16, 1927.



from the smallest visible up to 2 cm. or larger in diameter. The smaller calculi may produce the "mottled" cholecystogram which is indistinguishable from that of multiple papillomata. Those dark-filling defects of the visualized gall bladder have to be differentiated from overlying bubbles of intestinal gas. Fortunately, this is usually colonic, with something of a haustral pattern, and lies at a lower level than the gall bladder. If the gas is in the duodenum it becomes more of a stumbling block to interpretation. In either location the difficulty of distinguishing between non-opaque stones and collections of gas decreases as one's experience grows. The presence and persistence of colonic gas in the hepatic flexure and

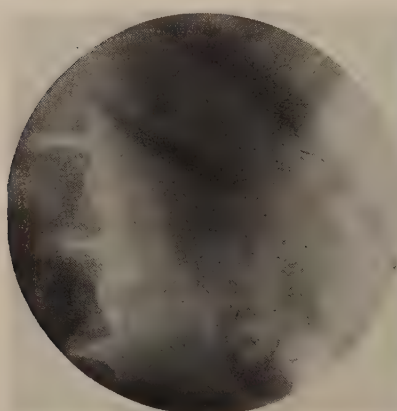


FIG. 162

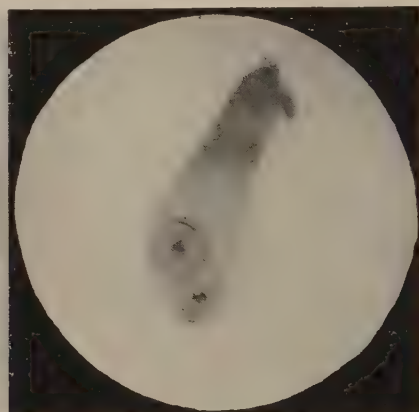


FIG. 163

FIGS. 162 and 163.—A rare type of partially non-opaque stone. Fig. 162: Cholecystogram. Fig. 163: Radiograph of excised gall bladder. The calculi have a calcium periphery and center.

its environs and the unsuccessful attempts to get rid of it, gave such an impression of its pathological significance that its occurrence was tabulated in 1218 examinations. The cholecystograms were normal in 615 and pathological in 603 of these. Forty-nine per cent of the former and 68 per cent of the latter had gas collections. The impression of its significance was probably erroneous, and the figures mean nothing.

An example of non-opaque stones is seen in Fig. 164. This patient had slight digestive disturbance. The cholecystogram revealed a functionally efficient gall bladder containing stones. As the patient had lues and was not greatly inconvenienced by alimentary symptoms, the gall bladder was not operated on. A

year later there was a characteristic subacute cholecystitis. Cholecystography resulted in a non-visualization of both the gall bladder

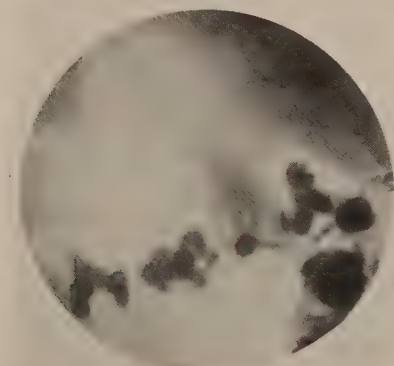


FIG. 164.—Example of multiple non-opaque stones.

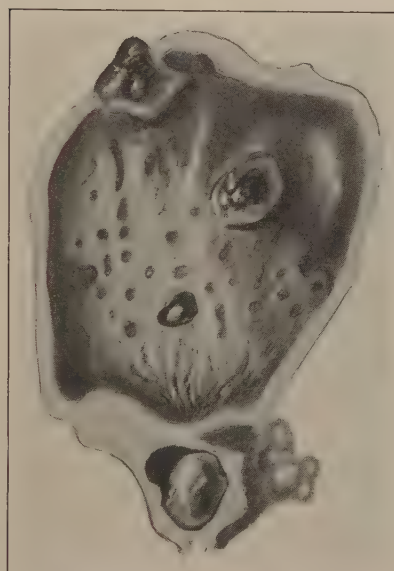


FIG. 165.—Cholecystectomy a year later. Drawing of opened gall bladder.

and the stones. Cholecystectomy was performed, and Fig. 165 indicates the severity of the cholecystitis and the nature of the calculi. In the sum total of our work stones have been seen in the

course of cholecystography in but 65 (3.8 per cent) instances in 1650 examinations. Calcium was present in 38 and absent in 27 of these stones. In all of the latter the dye was well concentrated in the gall bladder, while in only 8 of the former was it observed,

FIG. 166

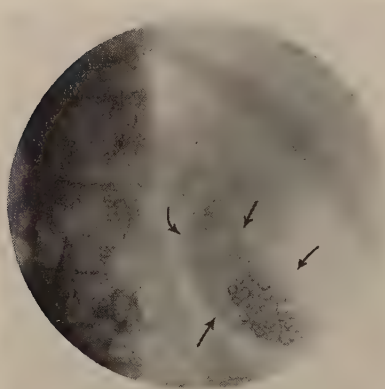


FIG. 167

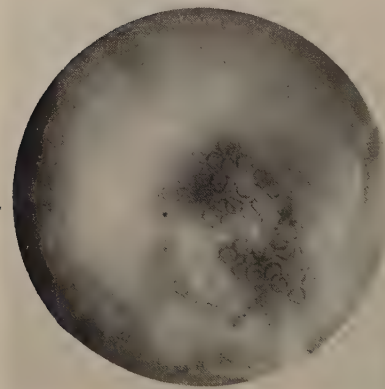
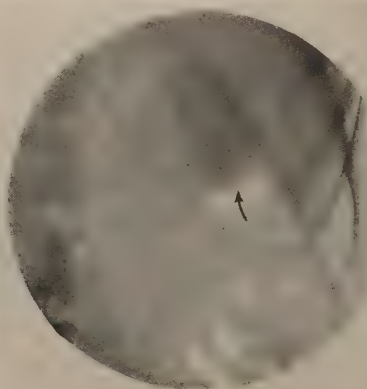


FIG. 168

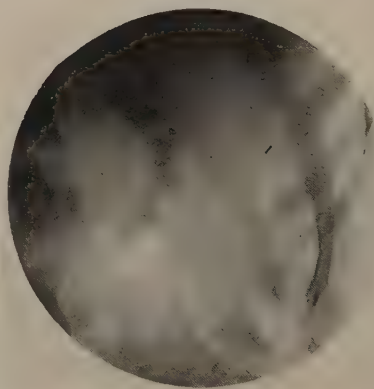


FIG. 169

FIGS. 166, 167, 168 and 169.—FIG. 166: Multiple calcified gall stones. Arrows indicate the dye-filled gall bladder. (Reproduced through the kindness of Dr. Oscar Zink, St. Luke's Hospital, St. Louis, Mo.) FIG. 167: Very fine calcified gall stones, with good concentration in the gall bladder. FIGS. 168 and 169: Calcified gall stones, without any dye present. FIGS. 166, 167, 168 and 169 indicate behavior of gall bladder in the presence of calcified stones.

and in these visualization was just great enough to permit the statement that it had occurred. Cholecystectomy was performed on 203 of the patients examined and calculi were found in 97 of them. Stones were not observed in the cholecystograms in 70 instances

in which they were actually present. In this group there was non-visualization of the gall bladder in 53 and faint visualization in 17. Obviously these stones were of the non-calcified type. *On practically every occasion where soft stones were found at operation, they were diagnosed previously by cholecystography, except in those cases where no visualization of the gall bladder had resulted.* Non-opaque ("negative" or "cholesterol") calculi with normal or nearly normal density of the gall bladder in the cholecystograms were found on 10 occasions. There were 17 cases with calcified stones, *i. e.*, with sufficient calcium content to permit of their visualization by simple radiography, with non-visualization in 13 and faint visualization in 4 instances. (Figs. 166, 167, 168, 169.) These results are summarized in the appended table:

TABLE I.  
203 Cholecystectomies.

Non-opaque stones at operation not found in cholecystograms:	
Non-visualization of the gall bladder . . . . .	53
Questionable visualization of the gall bladder . . . . .	17
Non-opaque stones at operation found in cholecystograms:	
Non-visualization of the gall bladder . . . . .	0
Faint visualization of the gall bladder . . . . .	0
Clear visualization of the gall bladder . . . . .	10
Opaque stones at operation found in cholecystograms:	
Non-visualization of the gall bladder . . . . .	13
Faint visualization of the gall bladder . . . . .	4
Clear visualization of the gall bladder . . . . .	0
<hr/>	
Total cases of lithiasis . . . . .	97
Non-calculous cholecystitis . . . . .	94
Pericholecystitis with some degree of cholecystitis . . . . .	12
<hr/>	
Total . . . . .	203

It is seen, therefore, from the above table that of the 80 cases in which non-opaque stone was found at operation, in only 10 (12.5 per cent) was there certain cholecystographic evidence of their presence. In contrast to this finding, however, is the fact that in every one of them (100 per cent) there was cholecystographic evidence of an abnormal gall bladder. It is very important to emphasize this fact strongly because there is too great a tendency on the part of some writers to fail to realize that after all cholecystography is a test of function of the gall bladder, and that it gives definite specific evidence of disease only incidentally. We do not feel that the diagnostic value of the procedure for clinical use is diminished thereby, but on the contrary, it is increased because disturbed function of an organ is usually the earliest and certainly one of the most dependable signs of disease, whether that be inflammation, neoplasm, abnormal metabolism or what not.



In our experience calcium-containing stones found in the course of cholecystography have invariably been demonstrated in a subsequent examination without the dye. It is difficult to reconcile this fact with the statements of other workers that the dye may conceal stones. The foregoing observations should be contrasted with those of Mateer and Henderson<sup>1</sup> and Camp, *et al.*,<sup>2</sup> among others.

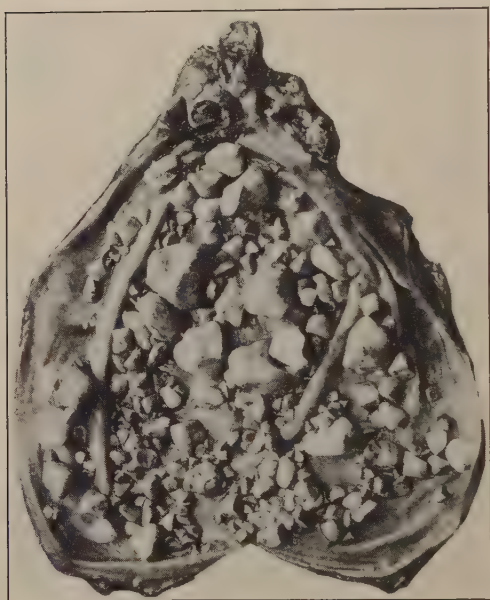


FIG. 170



FIG. 171

FIGS. 170 and 171.—Two examples of gall bladders containing non-opaque stones. Non-visualization of both gall bladder and stones. This is a frequent type of cholelithiasis where non-visualization is observed.

Our figures make it clear that indirectly cholecystography is enormously valuable in discovering biliary calculi and that actual visualization of stones is of minor importance. (Figs. 170 and 171.) The experience with calcified stones indicates that preliminary raying should precede cholecystography. In cholelithiasis, if non-opaque stones are observed after the oral administration of the dye, the interpretation is the same as would be the case with the intravenous method. Neither method is of much value in the cases with opaque stones.

<sup>1</sup> Mateer, J. G. and Henderson, W. S.: Chronic Biliary Tract Disease, Arch. Int. Med., vol. 33, No. 6, p. 728.

<sup>2</sup> Camp, J. D., Reeves, R. J. and Field, Henry, Jr.: Experience with Cholecystography, Boston Med. and Surg. Jour., vol. 194, No. 21, p. 976.

**Persistence of Gall-bladder Shadow.**—If the gall bladder is well visualized in the cholecystograms, ingress of the dye-laden bile must be free; we consider that egress is equally free, as it seems that, with the exception of certain fluid elements, the contents of the organ

FIG. 172



FIG. 173

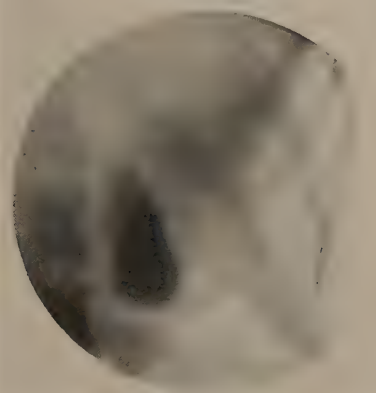


FIG. 174

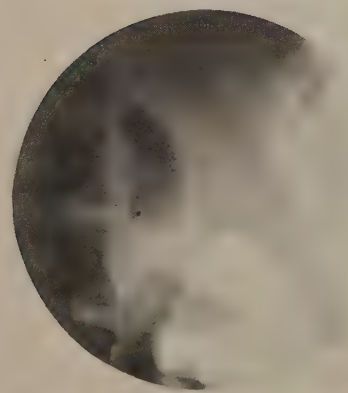


FIG. 175

FIGS. 172, 173, 174 and 175.—Illustrating persistence of dense gall bladder shadow. Normal subject. Intravenous administration of dye. Fig. 172: Four hours. Fig. 173: Eight hours. Fig. 174: Twenty-four hours. Fig. 175: Thirty-two hours after injection. In this case persistence of shadow clearly due to lack of food intake.

reach and leave it by the same route, that is, the cystic duct. Therefore, if the image of the gall bladder is observed at examinations at later hours than it is seen in normal cases, an explanation aside from disease of the vesicle is to be sought for. In such an event

either the gall bladder does not evacuate its dense contents or they are replaced as rapidly as they leave the organ. Our observation leads us to believe that prolongation of the period of abstention from food most commonly produces this finding, particularly after the dye has been given by vein. (Figs. 172, 173, 174 and 175.) Undoubtedly in some instances there is reabsorption of the dye from the intestinal canal. If alimentary administration is resorted to the larger amount of dye given could readily account for this occurrence. In either of the last two contingencies there is a continuous replacement of the dense bile as rapidly as it leaves the gall bladder. Whatever the cause of a persistent image of the organ may be, there is as yet no reason to consider this finding as evidence of cholecystitis.

**Excessive Size of Gall Bladder.**—This is an observation that we have not yet had an opportunity to encounter, though it has been mentioned by others. The most certain cause of enlargement of the gall bladder is obstruction of the common or cystic ducts. In the cases of the former, dilatation is brought about by bile retention, and in the latter by the same agency and by accretion of those substances secreted by the mucous membrane lining the vesicle. The gall bladder is frequently found greatly enlarged and dilated and full of stones, yet with the ducts patent. In none of the above conditions do we consider that bile concentration is possible and hence there would be a non-visualization of the gall bladder cholecystographically. Cyst of the gall bladder, or the ducts, which may attain large size, is an extremely rare condition and is illustrated on page 195. If such cysts possess the capacity of concentrating bile, it is possible that they could account for large gall-bladder images observed in cholecystograms. Such a thing is, however, a curiosity and merits only theoretical consideration. Gall-bladder images may vary 200 or 300 per cent in size, following the reasons that have been given before, and yet be entirely normal. If well visualized, size is *per se* of no diagnostic import.

## SECTION VII.

### THE DIAGNOSTIC EFFICIENCY OF CHOLECYSTOGRAPHY.

**The Principal Application of Cholecystography.**—In the pathological biliary tract cholecystography supplies directly but little information save as to the condition of the gall bladder itself.

Combined with the liver-function test described by us,<sup>1</sup> valuable data relating to the state of that gland may be obtained. However, the condition of the ducts is not disclosed by this means. In contradistinction to the foregoing, we believe that normal cholecystographic behavior eliminates the biliary tract as the offender in a case for differential diagnosis. Several writers disagree with this opinion, and Eusterman<sup>2</sup> quotes Kirklin to the effect that in 121 cases of cholecystitis and cholelithiasis 37 of the cholecystograms were normal.

Over-concentration of the bile in relation to cholecystography has been mentioned previously. It is supposed to accompany papillomatous disease of the gall bladder. If an excess of fluid is removed from the contents of this organ, in all likelihood it would arise just from this condition. With the development of papillomata the absorbing surface of the vesicle is naturally increased in area. We have had no experience with the over-concentration of the bile, as has been stated before, and we have as yet not encountered a papillomatous gall bladder.

Of the pathological processes involving the gall bladder, inflammatory disease is the one par excellence for the application of cholecystography. Inflammation is virtually always present in cholelithiasis, so the latter is included in the inflammatory states. Parasitic infestation of the gall bladder in all probability will present a sufficient degree of inflammation that concentration of the bile would be interfered with or prevented to such an extent that the organ could not be visualized. We have neither had experience with such conditions nor found reports of a test being carried out in such a case.

**Cholecystography in Tumor.**—Cholecystography has done little in discovering tumors of the gall bladder. The only report bearing on this is that of Carman,<sup>3</sup> who found multiple papillomata in 1 case. Carcinoma involving the gall bladder and the ducts, in our operative material, was found on 5 occasions. In all of these there was non-visualization of the vesicle. As carcinoma of this organ originates so frequently on a basis of chronic irritation or inflammation and would probably give rise to such a state (where it had not existed before) in a relatively short time, it is highly probable that the car-

<sup>1</sup> Graham, E. A., Cole, W. H., Copher, G. H. and Moore, S.: Cholecystography: Use of Phenoltetraiodophthalein, *Jour. Am. Med. Assn.*, 1926, **86**, 1899.

<sup>2</sup> Eusterman, G. B.: Cholecystography: A Clinical Appraisal, *Proceedings of the Staff Meetings of the Mayo Clinic*, 1927, **2**, 188.

<sup>3</sup> Carman, R. D.: The Roentgenological Diagnosis of Cholecystic Disease, *Am. Jour. Roentgenol.*, 1924, vol. **12**, No. 5.



cinomatous gall bladder will never be visualized. Theoretically this should be the case with either the fungating or diffusely infiltrating type of neoplasm. If the cholecystograms presented a constant marginal filling defect distinct from that of the cholesterol stone, one would be justified in speculating that it was produced by a tumor projecting into the cavity of the viscus. The discovery of such an hypothetical case could only be regarded as an accident, for the reason that there would probably be no symptoms sufficient to demand examination of the biliary tract. Though chronic irritation is hardly as important a predisposing factor in the other malignant tumors of the vesicle, it is probably just as frequently a sequence to their presence as is the case with carcinoma. The probabilities are that the same will hold true in a case of the benign neoplasms. On the whole, it appears that cholecystography promises little in the specific diagnosis of tumor.



FIG. 176.—Patient had had cholecystostomy eight years before. Cholecystography showed a well-preserved function of the gall bladder, and the symptoms were found to be due to disease elsewhere than in the gall bladder. (Reproduced through the kindness of Dr. Oscar Zink, from St. Luke's Hospital, St. Louis, Mo.)

#### **Cholecystography in Postoperative Condition of the Gall Bladder.**

—We have applied this test to a few cases which have had previous operations either on the vesicle or its ducts. One case (Fig. 176) had a cholecystostomy and drainage eight years before. A very good function was preserved, and the symptoms which led to the examination were ascribed to disease elsewhere. In another case there had been a drainage, followed later by what was said to be a cholecystectomy, but in which, in fact, the fundus only had been amputated. There was partial function of the remnant of the gall

bladder, enough to warrant the opinion that it was pathological, which after removal it proved to be. All the other cases of an antecedent operation that we have had resulted in a non-visualization of the gall bladder. In this connection the article by Spurling and Whitaker<sup>1</sup> should be referred to. They were unable to demonstrate a normal cholecystogram in 12 patients who had had a previous cholecystostomy. It has been shown that with bile retention from duct obstruction, the gall bladder will not be visualized and we therefore omit the test. It should be omitted also if there has been a cholecystectomy and the history of such an operation is clear. If there is a persistent biliary fistula following an operation on the gall tract, its injection with an iodized oil or other fluid opaque



FIG. 177

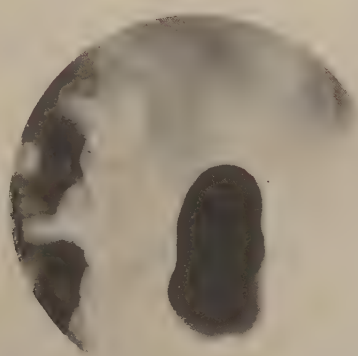


FIG. 178

FIGS. 177 and 178. —Persistent biliary fistula. FIG. 177: Arrow indicates opaque body, probably a stone in cystic duct. FIG. 178: Gall bladder filled with sodium bromide solution.

contrast medium will be most useful in discovering the cause for the presence of such a fistulous tract. This application of a contrast medium has been dealt with in the section dealing with the dyes used in cholecystography. Figs. 177 and 178 illustrate what can be accomplished by this manœuvre.

The question has been asked, might the ducts take on the function of concentrating bile, and, in the absence of the gall bladder, might they not be demonstrated by cholecystography? The answer is to be found in the chapter on Physiology, and in addition to the reasons there advanced, if the duct system does take on the concen-

<sup>1</sup> Spurling, R. G. and Whitaker, L. R.: End-results of Cholecystostomy as Shown by the Cholecystogram, Surg., Gynec. and Obst., 1927, vol. 44, No. 4, Pt. II.

trating function the volume of dye-filled bile present in them is scarcely great enough to produce an image.

**Functional Disorders of the Gall Bladder Aside from Concentration.**—In the chapter on Diagnosis reference is made to possible functional disturbance of the gall bladder distinct from concentration. It seems reasonable to suppose that in the case of the gall bladder of the asthenic there might be a disturbance of that organ analogous to that observed in the kidney in this type of individual. The kidney may prolapse, kink the ureter, and cause various symptoms. As the contents of the gall bladder reach that organ and leave it by the same passageway, that is, the cystic duct, one does not observe in the case of the vesicle any phenomenon similar to a Dietl crisis. The reason for this is clear. However, if the cystic duct should become kinked because of a pendulous gall bladder, its contents could not be released nor could they be added to. The same would be true with an intermittent torsion of the organ. It does not seem excessively ingenious to suppose that if such conditions occurred there might be found well-defined symptoms of cholecystitis or possible gall-bladder colic, without actual organic disease being present. These observations suggest that in an asthenic with slight symptoms of gall-bladder disease, posture during gastric digestion might be regulated in such way as to be a valuable aid to dietetic and other treatment. If there is a rapid emptying of the gall bladder there might, in the sthenic, be digestive symptoms following. This is a question which might be profitably investigated, especially in the light of the supposititious predominance of cholecystic disease in large people.

In the present state of our knowledge, cholecystography does little except to suggest the possibility of functional or possibly metabolic disturbance of the gall bladder. It does, however, seem to indicate that individuals with obscure digestive symptoms and without demonstrable organic disease in the alimentary tract may have the origin of the disturbance in slight aberrations in some of the unknown activities of the gall bladder.

**Cholecystography in the Young.**—Gall stones and cholecystitis rarely occur in childhood. However, their incidence in that period, now that there is a means of determining it, will probably prove to be higher than hitherto taught. We have had occasion to apply the test to a few children, and find that the procedure is the same in all respects as when carried out on adults, except for the decrease of the dose of dye, as would be the case in the administration of any other drug or chemical. Cholecystitis must in many instances have

its origin in adolescence or early adult life. It has been called a disease of this period with middle-age manifestation. The writers are of the opinion that more cases in this age period should be examined to determine the existence of such early disease, now that we have the means of diagnosing it. They feel that this should be the case especially where there are either obscure appendiceal symptoms, transitory jaundice, or any generalized infection, if digestive symptoms ensue. Then cholecystography could be carried out advantageously and the early diagnosis of cholecystitis might be established. In other words, besides securing more accurate information in regard to the early diagnosis of disease of the gall bladder, if young persons are tested by this means, it appears that valuable information in regard to the pathogenesis of this affection might be discovered. This in turn might lead to prevention of cholecystitis or a better means of treating the condition after it has developed.

**Cholecystography in Differential Diagnosis.**—The subject of differential diagnosis is covered in the chapter dealing with diagnosis of biliary-tract disease; hence it will only be mentioned at this point. Fuller discussion is necessary in connection with those conditions in which other roentgen-ray procedures are required. The latter pertain to the roentgen-ray examination of the gastro-intestinal and right urinary tracts.

This test is extremely useful in cases of chronic heart disease and angina pectoris, but before applying it, one should be assured that the patient's condition is such that it is safe to administer the cholecystographic dyes. We have observed brilliant results in cases of heart disease following cholecystectomy, in which cholecystography had revealed a pathological gall bladder. We know of suspected cases of angina pectoris receiving complete and permanent relief following cholecystectomy after it had been determined that there was a pathological gall bladder. In those pathological conditions which may be ascribed to a hidden focus of infection, cholecystography will often reveal a diseased gall bladder which is symptomless. We have known cases of chronic arthritis relieved by cholecystectomy after the presence of diseased gall bladder was established, just as occurred in the cases of heart disease. Where all other sources of focal infection have been eliminated, this test can be carried out to great advantage. Differentiation of spinal disease and chronic cholecystitis is considered in the chapter on Diagnosis. In rather rare instances disease of the spinal column presents symptoms indistinguishable from those found in vague cases of cholecystitis. Naturally, cholecystography is not



the means for discovering such spinal disease. However, in all cases all portions of the spine or ribs which appear in cholecystograms should be carefully scrutinized for evidence of involvement. An example of this confusion, the diagnosis being cleared up through this test, is shown in Figs. 179 and 180. In this connection it may be said that cholecystography is occasionally useful in determining whether a tender point is in the gall bladder or outside of it. We are of the opinion that if there is a pathological condition causing the gall bladder to be tender, the probabilities are that it could not be visualized. This, however, does not do away with the usefulness of the test in the process of elimination.

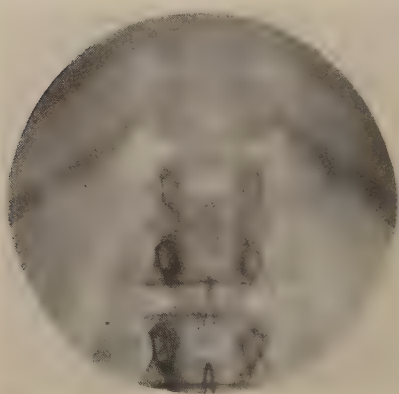


FIG. 179

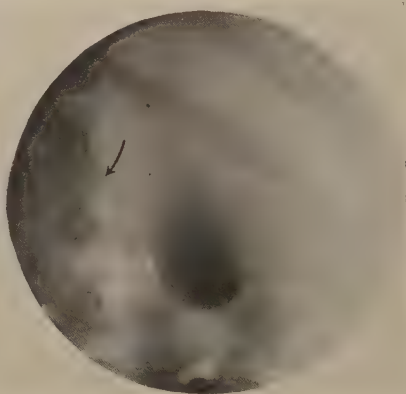


FIG. 180

FIGS. 179 and 180.—Fig. 180: Normal cholecystogram of patient supposed to have chronic cholecystitis because of pain in gall-bladder region. Arrow indicates suggestive spinal disease. Fig. 179: Film of spine indicates characteristic tuberculosis of spine.

**Cholecystography in Diseases of the Alimentary Tract.**—Cholecystography may be employed in conjunction with the opaque meal. (Figs. 181, 182 and 183.) In this compound procedure, of course, the dye precedes the barium in administration. However, ingestion of the latter may result in the non-appearance or the disappearance of the gall-bladder shadow for reasons which have already been given. In the vast majority of cases two independent examinations on successive days are preferable and will give satisfactory results.

There is a certain small proportion of atypical deformities of the duodenal bulb which one is justified in considering due to intrinsic disease, ulcer. Since the advent of cholecystography we have

found in a few cases that these deformities have been produced by a diseased gall bladder. These observations explain those cases which in the past were diagnosed as duodenal ulcer and in which, at operation, the radiologist was considered to be in error because a

FIG. 181

FIG. 182

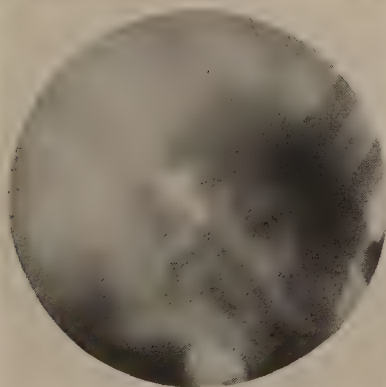
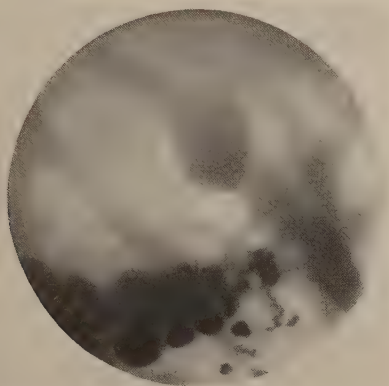


FIG. 183

FIGS. 181, 182 and 183.—Illustrates combined use of opaque meal and cholecystography. The former has preceded the latter in administration.

diseased gall bladder, and not a duodenal ulcer, was found. Cholecystography, therefore, will serve to make the diagnosis of duodenal ulcer more accurate than it has been. It is quite possible that in a rare case a similar confusion might arise in respect to gastric ulcer and cholecystitis in which the difficulty might be resolved by resort

to cholecystography. Likewise, disease of the hepatic flexure could be similarly made clear, though here we lack experience.

The condition known as duodenal stasis, or ileus, is beginning to be understood. Symptomatically it may simulate chronic chole-

FIG. 184

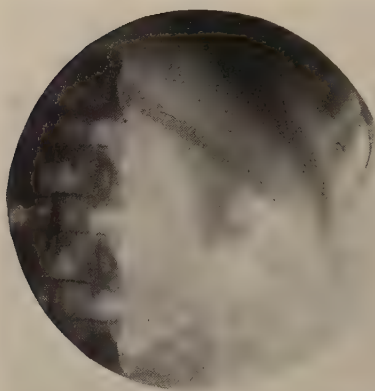


FIG. 185

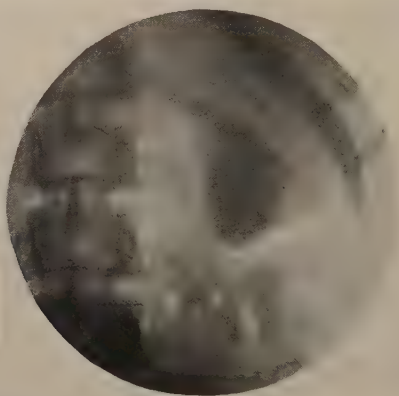


FIG. 186

FIGS. 184, 185 and 186.—Cholecystograms which are normal, in a patient upon whom a clinical diagnosis of cholecystitis was made, but whose symptoms were really due to intestinal allergy. With the spastic condition of colon, pain was referred to the gall bladder region. See Figs. 187, 188 and 189.

cystitis very closely. It is quite possible that it may in its later stages give rise to the latter. It is not an easy condition to discover with the usual gastro-intestinal examination and the findings, certainly in the early phases of the affection, may be extremely doubtful. Duodenal stasis is very disabling, and with proper

surgical treatment good results are obtainable. Cholecystography may be most useful in differentiating between this condition and chronic cholecystitis.

FIG. 187

FIG. 188

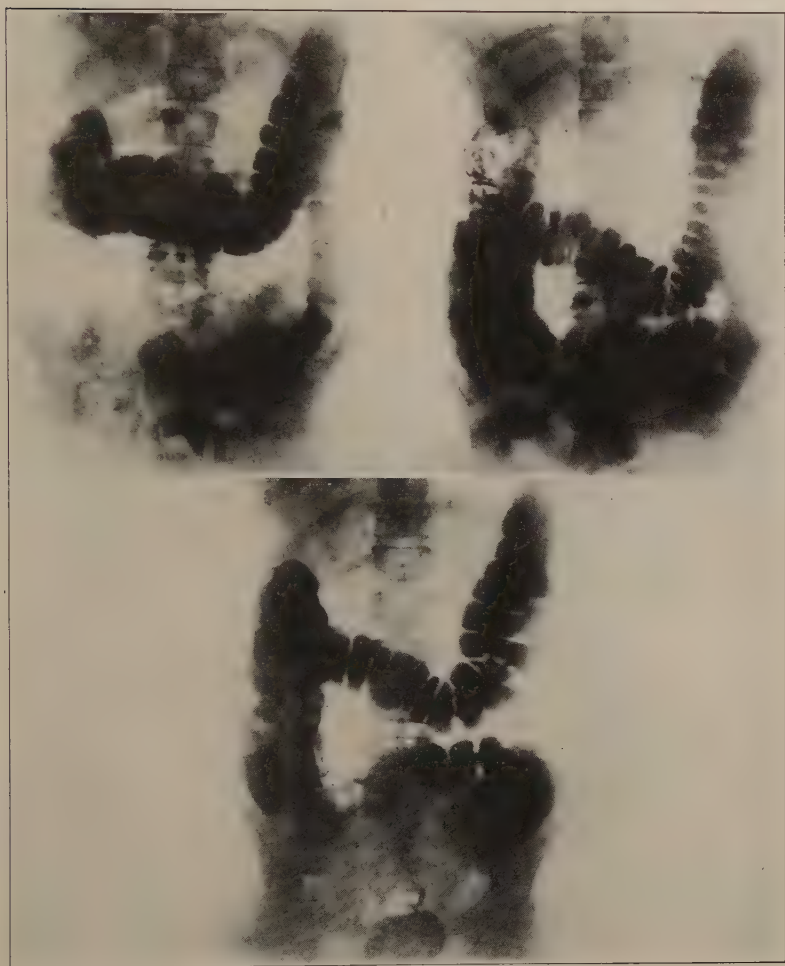


FIG. 189

FIGS. 187, 188 and 189.—Barium enema films of same case of Figs. 184, 185 and 186. Patient sensitized to wheat. Fig. 187: Condition of colon after withdrawal of wheat from food. Fig. 188: Condition of colon after administration of wheat. Note extreme spastic haustration of transverse colon. Fig. 189: The same patient five minutes later, after administration of epinephrine. Note the change of haustral pattern.



There are rare cases of intestinal allergy in which pain and tenderness may occur in the right upper abdominal quadrant in such a way as strongly to suggest disease in the biliary tract. Such a case was brought to our attention through the kindness of Dr. Charles H. Eyermann. The pain in the gall-bladder region in this case was so severe that cholecystography was carried out and a normal gall bladder was discovered. (Figs. 184, 185, 186.) It was found that this patient was sensitive to wheat. Figs. 187, 188 and 189 show the barium enema films on this case and are explained in the legend. This case illustrates that cholecystography may be useful in these conditions, as rare as they are.

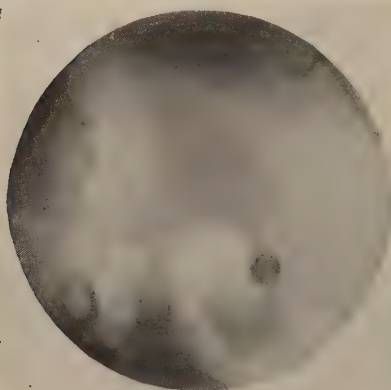


FIG. 190

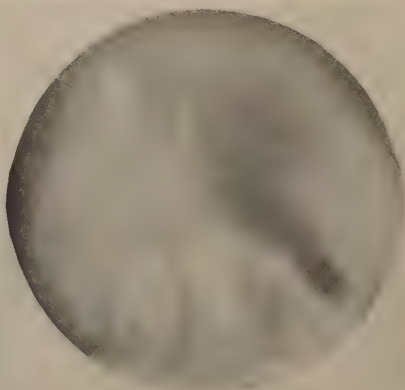


FIG. 191

Figs. 190 and 191.—Illustrates an unusual type of gall stone. Fig. 190: Open film. Pyelography could not determine the location of this dense body. Fig. 191: Cholecystography reveals it to be a gall stone; confirmed at operation.

**Cholecystography in Disease of the Right Urinary Tract.**—As has been indicated, there is frequently confusion between kidney and gall bladder in the diagnosis of disease of the right upper abdominal quadrant. This is particularly the case where an opaque body has been shown on films of the region, and the points of distinction outlined on page 237 are deviated from. We have also shown that even pyelography will not always determine the nature of such a finding. It is here that cholecystography will clarify matters, as is seen in Figs. 190 and 191. Chronic cholecystitis may be extremely difficult, or sometimes impossible, to differentiate from chronic infectious processes of the kidney and its pelvis. Further, the two conditions may coexist. (Fig. 192.) It is possible that occasionally one process originates the other. Cholecystography could, under

certain circumstances, determine whether the offender was the gall bladder or the kidney. It might reveal which condition was in the greatest need of treatment. Certainly chronic cholecystitis and pyelitis may be very much alike, and the commonly held views of both conditions appear to be entirely too orthodox. L. G. Cole and George<sup>1</sup> have drawn this parallel and said that "it is no more to be expected that roentgen-ray findings will comport with the classical picture of gall-bladder disease than will the roentgen-ray findings and classical symptoms in renal disease." There is indeed much similarity between disease of the two organs. The evolution of the roentgen-ray examination of the two is also not unlike. At one time the roentgen-ray examination of the urinary tract was almost wholly



FIG. 192.—Concurrent existence of gall stones and pyelitis; slight degree of hydro-nephrosis. Lower arrows indicate stricture of the ureter; upper arrow indicates a stone, probably in cystic duct.

centered on the demonstration of calculi. With the development of pyelography, this search has been relegated to one of comparative unimportance, when considered in the light of the large volume of pyelography that is done.

Where both gall stones and kidney stones are found in the same patient they often constitute a problem in treatment which is most difficult to solve. Cholecystography may to some extent point to the proper measures to be employed. Fig. 193 is an illustration of what was thought to be concurrent presence of gall stones and kidney stones. The test in this case determined the diagnosis by proving that all the stones were intrarenal. Though it probably does not

<sup>1</sup> George, A. W. and Cole, L. G.: *The Roentgen Diagnosis of Gall Stones by Improved Methods*, Boston Med. and Surg. Jour., vol. 172, p. 326.

fit exactly in this connection, the visualized gall bladder can assure one that a calcification or other dense body is not a gall stone.

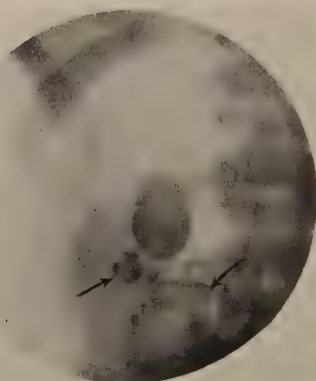


FIG. 193.—Multiple right renal stones. Normal gall bladder. The left arrow indicates kidney calculi, thought to be gall stones; right arrow indicates a pelvic stone.

**Summary and Conclusions.**—Unreinforced roentgen-ray procedures will discover the pathological gall bladder in its late stages in a certain percentage of cases. In acute and early chronic cholecystitis they are practically useless. But it is this group of cases that one must attack if our methods of dealing with cholecystitis are to give improved results. The older roentgen-ray procedures do not furnish us with any information in respect to either improved treatment or prevention. Cholecystography in the hands of various writers has an accuracy ranging from 80 to about 97 per cent, indicating its superiority over former methods, as shown by the table on page 331, compiled by one<sup>1</sup> of the writers:

These figures, however, are no measure of the advantage afforded the patients, not only in greater accuracy, but for the earlier diagnosis and intervention. Its advantages, furthermore, which are not reducible to figures, are in pointing the way toward prevention and possibly treatment in the early phases of cholecystitis where mutilation by operation might in time be found unnecessary.

Some idea of the diagnostic superiority of cholecystography over simple roentgen-ray examinations may be gathered from the following: In the eight years preceding the discovery of cholecystography

<sup>1</sup> Graham, E. A.: *The Present Status of Cholecystography, and Remarks on the Mechanism and Emptying of the Gall Bladder*, Surg., Gynec. and Obst., February, 1927, p. 153.

TABLE II.—CASES REPORTED IN WHICH CHOLECYSTOGRAPHIC EXAMINATION HAS BEEN COMPARED WITH OPERATIVE FINDINGS.

Author.	Method of administration.	Diagnosis of normal gall bladder.			Diagnosis of pathological gall bladder.			Total percentage of correctness of diagnosis.
		Normal gall bladder at operation.	Pathological gall bladder at operation.	Percentage of correctness of cholecystography.	Normal gall bladder at operation.	Pathological gall bladder at operation.	Percentage of correctness of cholecystography.	
Sosman, Whitaker and Edson	Intravenous	4	1	80.0	1	37	97.3	95.4
Carman	Intravenous	0	9	0	0	41	100.0	78.0
Carman	Oral	21	18	53.9	0	103	100.0	87.3
Cohen and Roberts	Intravenous	2	0	100.0	1	7	87.5	90.0
Wilkie and Illingworth	Intravenous	21	2	91.3	0	32	100.0	96.4
Gosset and Loewy	Mostly intravenous	21	0	100.0	1	10	91.0	96.9
Stewart and Ryan	Oral	1	0	100.0	2	21	91.3	87.5
Jewett	Oral	2	0	100.0	1	10	91.0	92.4
Winslow and Melgard	Intravenous	1	0	100.0	0	6	100.0	100.0
Nemours-Auguste	Intravenous	3	0	100.0	0	5	100.0	100.0
Kaznelson and Reimann	Intravenous	1	0	100.0	0	3	100.0	100.0
McCoy and R. S. Graham	Intravenous	8	0	100.0	0	16	100.0	100.0
McCoy and R. S. Graham	Oral	0	0	....	0	2	100.0	100.0
Totals of others	.....	....	....	74.0	....	....	....	98.0
Graham, Cole, Copher and Moore	Mostly intravenous	....	....	....	4	143	97.3	97.3

Percentage of correctness in 446 cases of all authors with a diagnosis of pathological gall bladder, 97.8.

Percentage of correctness in 115 cases of all authors with a diagnosis of normal gall bladder, 74.

Percentage of correctness in 380 cases of all authors by intravenous method, 95.

Percentage of correctness in 181 cases of all authors by oral method, 89.



our roentgen-ray department reported gall stones on 85 occasions. But 33 of these were submitted to operation, and in all but 1 stone were found. This gives the very creditable percentage of 97 for preoperative diagnosis. However, in the same period there were 72 cases with negative roentgen-ray reports in which operation revealed cholelithiasis on 42 and cholecystitis on 30 occasions. Combining these figures, the diagnostic efficiency sinks to 30+ per cent. This should be contrasted with the 97.2 per cent efficiency for cholecystography. Since its advent, cholecystectomy in our hands has shown a decrease of 15 per cent in the number of cases with stones. This is highly suggestive that an earlier diagnosis has been attained.

In what is to follow, it is assumed that the dye has been administered intravenously and that this and the roentgen-ray technique have been carried out correctly. If alimentary introduction has been employed the cautions that have already been pointed out should be observed.

We will here recapitulate and discuss briefly, in the order of their importance, our criteria for interpreting cholecystograms:

1. If the gall bladder fills, concentrates, alters in size, and empties, as has been described, we believe that it is normal, regardless of the method by which the dye was given. The capacity to estimate normal concentration is gained by experience. Certain observers, among them Eusterman<sup>1</sup> and Mateer and Henderson<sup>2</sup> hold that a pathological gall bladder may present normal cholecystograms. Our experience in this regard is limited to 1 case, in which, because the clinical outweighed the cholecystographic evidence, an operation was performed. Cholecystectomy revealed a normal gall bladder and the patient retained his symptoms. There were 5 cases in which there was divergence of opinion between the radiologists and the clinicians as to the interpretation of the cholecystograms. The gall bladders were found pathological after cholecystectomy. These cases might be considered as examples of a rare occurrence of normal cholecystographic behavior in a pathological organ.

2. If there is non-visualization of the gall bladder (due consideration having been given to the extra-cystic factors that have been previously described), it is pathological, in our experience, in 100 per cent of 100 operative cases.

<sup>1</sup> Eusterman, G. B.: Cholecystography: A Clinical Appraisal, Proceedings of the Staff Meetings of the Mayo Clinic, 1927, 2, 188.

<sup>2</sup> Mateer, J. G. and Henderson, W. S.: Chronic Biliary Tract Disease, Arch. Int. Med., vol. 33, p. 728.

3. The finding of non-opaque ("negative," non-calcified, or cholesterol) stones. Here one must beware of intestinal gas bubbles and repeat the test if in doubt. Since a gall bladder carrying such stones has a good concentrating function, and since the pathogenesis of such stones is enigmatic, one may justly speculate as to the state of the gall bladder prior to the stone formation. Is the viscus so inflamed that there are symptoms and pathological findings of cholecystitis? And do not such gall bladders account for the alleged pathological cases having normal cholecystograms? Our own experience does not indicate this. Every example of "negative" stones that has been operatively sought for has been found, a total of 10 cases.

4. Faint cholecystograms indicating impairment of concentration. This represents a step in the loss of that function of the gall bladder and is somewhat proportional to its involvement. This is a frequent and treacherous sign. Sixty-five such have been operated on and cholecystitis found in all of them.

5. Fixation and persistent deformity of the gall bladder, which we term pericholecystitis. If they occur with faintness of the shadow, they are reliable pathological signs. It is both infrequent and difficult to establish. This has been found 12 times at operation among 12 preoperative diagnoses.

6. Constancy of size of the cholecystograms is of slight importance unless coupled with lack of density. In that event it is an important finding.

7. Retarded appearance of the gall-bladder shadow. If the liver function approximates normal, this is a valuable but rare sign.

8. Persistence of the gall-bladder image is indicative of lack of food intake or of intestinal reabsorption of the dye. We are not yet clear as to its significance.

In conclusion, certain points which have been developed before and to which attention has been called by many writers should be reiterated. Cholecystography is an extremely accurate measure of the functional capacity of the gall bladder. This functional capacity is decreased in proportion to the intensity and duration of a disease process which may have involved it. Cholecystography is not a simplified means for the diagnosis of cholecystitis and cholelithiasis. It can be carried out properly only with painstaking care, and its requirements are exacting if reliable data are to be obtained by it. Cholecystography is not to be substituted for other diagnostic means, either radiological or physical. Final conclusion as to whether or not a gall bladder is normal cannot always be

drawn merely from its external appearance at laparotomy. In this connection see the chapter on Diagnosis. Cholecystography is therefore a more critical means of examination of the gall bladder than are inspection and palpation. Cholecystograms are to be interpreted in conjunction with the clinical facts pertaining to the individual case. Before a patient is submitted to this test he should be examined to determine his general condition.

Although we feel that a strong advocacy of any new method is an unscientific attitude and should therefore be avoided, we, nevertheless, think that we should call attention to certain fallacies in the criticism of cholecystography which have sprung up. One type of fallacy is that all who work with cholecystography are equally expert in their interpretations.

Another one is that symptoms from an organ are entirely dependent upon gross pathological lesions, when, as a matter of fact, of course, symptoms are always due to functional disturbances, which, however, are indeed usually traced to some demonstrable pathological evidence. This fallacy leads to conclusions which condemn the value of cholecystography because, on the one hand, a gall bladder diagnosed as having normal functions by cholecystography may show at operation perhaps a few old adhesions representing some healed process, and, on the other hand, a gall bladder may appear normal at operation in spite of a complete failure of concentrating function. If the gall bladder is functioning properly it is doubtful if it is causing symptoms at the same time, although the possibility that it may have caused symptoms in the past or will cause symptoms in the future cannot be excluded. On the other hand, one that is not functioning may cause symptoms despite an absence of any marked gross pathological changes.

Still another fallacy is concerned with the acceptance of the findings of pathologists who are not experienced in the interpretation of lesions of the gall bladder. A number of reports have appeared which state that the cholecystograms showed a normal concentrating power despite the fact that the excised gall bladder revealed a complete absence of the mucosa. Complete absence of the mucosa of the gall bladder from disease is an extremely rare condition which occurs only in complete gangrene. This fact has been particularly emphasized by Boyd, and his ideas harmonize with our own. The *apparent* frequency of the absence of the mucosa is, however, due to poor technique in the examination. Postmortem decomposition is very rapid in the gall bladder, and usually within a few hours after removal the mucosa will disappear unless the

specimen has been fixed. The finding of an absence of a mucous membrane is usually due to the fact that after the operation the gall bladder has been allowed to remain for several hours without fixation. Another explanation of an apparent absence of the mucosa is that if a small block of tissue is cut out of the gall bladder before fixation the mucosa retracts, and unless great care is exercised the subsequent microscopic sections will not reveal any mucous membrane.

Finally another fallacy is based on the idea that a gall bladder to be diseased must present the classical symptoms and signs which can be unequivocally recognized by the clinician. Thus, for example, Eusterman<sup>1</sup> of the Mayo Clinic, in a recent article emphasizing the limitations of cholecystography states that "the clinical history and physical examination, including the elimination of the stomach and duodenum as the site of disease by roentgen-ray examination, enables the experienced clinician to make a diagnosis of definite cholecystic disease in more than 90 per cent of the cases." Mentzer<sup>2</sup> also, in reporting studies made on material at the Mayo Clinic, states that "clinicians accurately identify a diseased gall bladder in about 85 per cent of the cases." It seems to us a bit inconsistent, however, that in another paragraph he states, "Of 1647 consecutive patients examined at necropsy, 37 per cent had cholesterosis of the gall bladder. Gall stones accompanied the lesion in 20 per cent of the cases. *Gall-bladder disease was not anticipated in most of these patients, for in 87 per cent of them the history of gastro-intestinal disease had been negative.*" (Italics ours.) In other words, without the use of cholecystography, it would seem that even such excellent clinicians as those at the Mayo Clinic really fail to recognize a very large percentage of diseased gall bladders. The proportion of error must be greater in places where the clinical skill of the examining physician is not on the same high plane. It is our opinion that a more extensive use of cholecystography will greatly reduce the high percentage of error which now occurs without this aid. Of course it is a simple matter to recognize by clinical methods those cases which present classical symptoms and signs, but our aim in diagnosis is ever to increase our ability to recognize the less obvious and the early disturbances. Probably also 90 per cent of the cases of carcinoma of the stomach can be recognized by clinical means alone if we wait for the classical signs to appear. But who wishes to advocate that plan?

<sup>1</sup> Eusterman, G. B. Limitation of Cholecystography with which Physicians Should be Familiar, Jour. Am. Med. Assn., 1928, **90**, 194.

<sup>2</sup> Mentzer, S. H.: The Status of Gall Bladder Surgery, Based on a Study of Fourteen Thousand Specimens, Jour. Am. Med. Assn., 1928, **90**, 607.



**Contraindications.**—The contraindications to its use because of physical conditions are few. There are none on the grounds of age. We have applied this test to patients aged from two to seventy years and, if indicated, we would carry it out at further limits than these. Patients with heart disease in a decompensated state and those who are subjects of arteriosclerosis, especially if the arterial tension is low, those with badly damaged livers and those with threatened uremia are not to be submitted to it.

If one employs this diagnostic means faithfully and carefully, his efforts will be rewarded with the knowledge that he has been of the greatest use to his patients. Careless, offhand application is a great disservice, and the test had better be entirely omitted unless meticulous care is employed.

## CHAPTER VIII.

### APPLICATION OF TESTS OF HEPATIC FUNCTION TO DIAGNOSIS OF BILIARY DISEASE.

THE close proximity of the gall bladder to the liver implies a direct physiological and pathological relationship, as well as an anatomical one. This relationship has been emphasized by some experiments conducted by one of us<sup>1</sup> in 1918, in which hepatitis was found to be practically a constant accompaniment of gall-bladder disease. It is discussed extensively in Chapter III. As a matter of fact the gall bladder is merely a part of the large biliary system, of which the liver is the chief component. The chief function of the gall bladder is to assist in the distribution of the bile as it is secreted by the liver.

The liver is the largest organ in the body, weighing about 1800 gm., and probably performs a greater volume of duties than any other organ. However, the well-known supposition of acceptance of the duties of one part of an organ by another part seems to apply strongly to the liver. Mann and Magath<sup>2</sup> have demonstrated that 70 per cent of an animal's liver rapidly replaces the part removed by operation. All of these factors emphasize the fact that the liver offers a large margin of safety for many physiological and pathological processes, because of its great reserve in so many of its functions.

#### FUNCTIONS OF THE LIVER.

**1. Carbohydrate Metabolism and Storage of Glycogen.**—This is probably the most important function of the liver. Monosaccharides are converted to glycogen in the liver, which in turn is called upon to reconvert the glycogen into dextrose for use elsewhere in the body. This glycogenic faculty was originally discovered by Claude Bernard in 1857. Perhaps an equal amount of glycogen is stored in the muscles, but the liver glycogen probably serves to maintain the blood-sugar level.

<sup>1</sup> Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, *Surg., Gynec. and Obst.*, 1918, **26**, 521.

<sup>2</sup> Mann, F. C. and Magath, T. B.: Studies on the Physiology of the Liver, *Arch. Int. Med.*, 1922, **30**, 73.

Adequate proof of the vital rôle in sugar metabolism maintained by the liver, is offered by Mann and Bollman<sup>1</sup> who found that when the liver is removed experimentally, the blood sugar rapidly falls to a very low level. The animal will become moribund, but if given glucose, will be restored to normal activity and may be kept alive thirty-four to thirty-six hours. Without injection of sugar, they found that death intervened in a much shorter time. Excision of the pancreas in addition to the liver merely accelerated the hypoglycemic reaction and rendered the glucose injections less effective.

2. **Protein Metabolism.**—The chemistry of this process is so complex that it is inadequately understood. However, evidence points to a conversion of ammonia, amino-acids and other nitrogenous products into urea by the liver. Bollman, Mann and Magath<sup>2</sup> demonstrated a decrease in the blood urea following removal of the liver and a rapid appearance of a substance which gives tests for uric acid. During the process of splitting of proteins by digestion, numerous amino-acids are formed. Some of these cannot be used directly by the body tissue and are converted by the liver into glucose and urea, the latter of which is eliminated by the kidneys.

The appearance of leucin and tyrosin crystals in the urine of patients having acute yellow atrophy of the liver is an indication of a loss of the power of proper deamidization. The experiments of Mann and his associates as mentioned in the preceding paragraph prove that the formation of urea ceases after hepatectomy; and if the animal becomes anuric, the amino-acids of the blood increase very rapidly. With the accumulation of uric acid in the urine they found large amounts of urates.

3 **Secretory Function.**—Insufficient knowledge of the liver is known at the present time to differentiate accurately the secretory and excretory products. However, it is generally agreed that the bile salts and bile acids are of secretory origin and form the chief components of that group of products. They accelerate greatly the action of the lipase from the pancreas, in splitting fats to fatty acids and glycerin, and aid in the absorption of the products of this hydrolysis. It is a well-known fact that in the absence of bile in the intestinal tract a large amount of the fat ingested passes through in the feces in an undigested state. The assumption that bile

<sup>1</sup> Mann, F. C. and Bollman, J. L.: Liver Function Tests, *Arch. Path. and Lab. Med.*, 1926, 1, 681.

<sup>2</sup> Bollman, J. L., Mann, F. C. and Magath, T. B.: Studies on Physiology of the Liver: VIII. Effect of Total Removal of the Liver on the Formation of Urea, *Am. Jour. Physiol.*, 1924, 69, 371.

salts originate from hepatic parenchyma receives support by the work of Whipple and his associates.<sup>1</sup>

4. **Excretory Function.**—Among the substances which seem to fall in the class of excretory products, bilirubin and cholesterol apparently are the most important. It is possible however to consider bilirubin as a secretory as well as excretory product. The significance of the formation and excretion of bilirubin can be realized when one recalls that the destruction of red blood cells is a constant source of bilirubin, most of which is eliminated by the liver under normal circumstances, as will be discussed elsewhere in this chapter. There are undoubtedly innumerable inert as well as toxic products absorbed in the intestinal tract which are of no value to the body mechanisms and are excreted as foreign bodies by the liver. Such products formed elsewhere in the body very probably reach the liver by way of the hepatic artery and are eliminated as waste.

5. **Pigment Metabolism.**—The Küpffer cells comprise the reticulo-endothelial system of the liver and are a source of bilirubin, although probably not as important in its formation as the bone-marrow, spleen, etc. (See p. 344.) The disposition of urobilin and urobilinogen, as they are absorbed from the intestinal tract, is left to the liver which converts them into bilirubin.

6. **Detoxifying Power.**—From the time of the pioneer work of Roger<sup>2</sup> it has been realized that from the standpoint of neutralization of toxic substances, there is no doubt that the liver offers one of the greatest protective mechanisms found in the body. Greene, Snell and Walters<sup>3</sup> have recently stated "the oxidation of indol to indoxyl and its ultimate excretion in the urine as indoxyl sulphuric acid; the conjugation of the toxic cholic acid with glycocholic and taurin to form glycocholic and taurocholic acids, which are excreted in the bile, and the formation and excretion of conjugated glucuronates are all evidences of this type of detoxification. The site of this detoxification is not known with certainty, but many of these changes are ascribed to the liver, and consequently there have been many attempts to secure a measure of the detoxifying power of the organism as an index of the functional activity of the liver."

The fact that poisons such as phosphorus and chloroform have a particular tendency to cause marked pathological changes in the

<sup>1</sup> Smythe, F. S. and Whipple, G. H.: Bile-salt Metabolism, *Jour. Biol. Chem.* 1922, **59**, 623.

<sup>2</sup> Roger, G. H.: Action due foie sur la strychnine, *Arch. de physiol. norm. et path.*, 1892, **4**, 24.

<sup>3</sup> Greene, C. H., Snell, A. M. and Walters, W.: Diseases of the Liver: I. A Survey of Tests for Hepatic Function, *Arch. Int. Med.*, 1925, **35**, 249.



liver, and produce practically no anatomical changes elsewhere, has been accepted as further evidence of the protective mechanism of the liver. Schirn<sup>1</sup> has found that a certain dose of atropine introduced into the peripheral circulation, produced no more effect than twenty times the amount would if injected into the mesenteric vein. This work is in accord with the much earlier work of Roger and others who noted the detoxifying action of the liver on many alkaloids. It has long been known that if particles of insoluble material, so finely divided that they can pass through the fine capillaries, are injected into the circulation, they will be fixed within the liver by phagocytic cells. One of us (Graham<sup>2</sup>) in 1915 reported evidence which indicates that the remarkable resistance of young pups to the development of chloroform necrosis of the liver is due to the large amount of glycogen in their livers.

The importance of the value of bile acids in detoxification is brought to our attention by Wells<sup>3</sup> who remarks that "compounds of many poisons are formed with bile acids which are insoluble, and therefore only slowly dissolve or decompose, thus protecting the body from overwhelming doses of the poison. Such compounds are formed, not only with inorganic poisons, but also with alkaloids, especially strychnine, brucin and quinine. They are then deposited in the liver to be slowly dissolved and eliminated."

A survey of the relation of the liver to detoxification and infection has recently been made by Opie<sup>4</sup> who concludes that the liver, by means of its peculiar endothelium lining its sinusoids, fixes insoluble material and many kinds of organic particles such as bacteria, etc. Arima<sup>5</sup> injected bacteria intravenously into rabbits and found that they disappeared from the blood in about one-half hour. They were found most abundant in the liver, and present in smaller numbers in the spleen and bone-marrow. Evidently the reticulo-endothelial system is a large factor in this detoxification process. Bull<sup>6</sup> found experimentally that immense numbers of bacilli were removed from the blood stream after injection. He injected a small portion of an agar slant of a culture of typhoid bacilli into the ear vein of a rabbit and found by culture methods that he could obtain

<sup>1</sup> Schirn: *Physiol. Rev.*, 1923, **3**, 41, cited by Gunn, J. A.

<sup>2</sup> Graham, E. A.: Resistance of Pups to Late Chloroform Poisoning in Relation to Liver Glycogen, *Jour. Exper. Med.*, 1915, **21**, 125.

<sup>3</sup> Wells, H. G.: *Chemical Pathology*, W. B. Saunders Company, Philadelphia, 1925, p. 270.

<sup>4</sup> Opie, E. L.: *Pathologic Physiology of the Liver and its Relation to Intoxication and Infection*, *Jour. Am. Med. Assn.*, 1925, **85**, 1533.

<sup>5</sup> Arima, R.: *Arch. f. Hyg.*, 1911, **73**, 265, cited by Opie.

<sup>6</sup> Bull, C. G.: The Fate of Typhoid Bacilli when Injected Intravenously into Normal Rabbits, *Jour. Exper. Med.*, 1915, **23**, 475.

from the liver, three minutes after the injection 12,000,000 colonies, fourteen minutes 6,000,000, one hour 700,000, two hours 80,000 and three hours 1000 colonies per cubic centimeter of crushed pulp.

**7. Relation of Liver to Coagulation of Blood.**—It is agreed that the liver exerts at least a partial influence upon the clotting elements of the blood, especially the fibrinogen content. But its exact rôle in the regulation of the fibrinogen content is not known.

In 1904 and 1905, Doyon and Kareff,<sup>1</sup> and Nolf<sup>2</sup> demonstrated that extirpation of the liver was followed by the rapid disappearance of fibrinogen from the blood stream. Several years later Whipple and Hurwitz<sup>3</sup> demonstrated a rapid fall of the fibrinogen content of animal's blood shortly after production of liver injury with chloroform anesthesia. The amount decreased from the normal variation of 0.2 to 0.5 gm. per 100 cc. of blood, to its minimum of 0.01 and even less, on about the second day following the anesthesia. The low figures persisted for two or three days and gradually began to rise until the normal fibrinogen content was reached on about the tenth day. Likewise, they found a low fibrinogen content of the blood (0.045 to 0.035 gm. per 100 cc. of blood) in patients with cirrhosis of the liver. In animals as well as humans with liver damage they found no significant change in the thrombin or calcium content of the blood.

In later work (1921) Foster and Whipple<sup>4</sup> discovered that tissue injury was perhaps the greatest known stimulus to the formation of fibrinogen, but they conclude "that all available data point to the liver as the only potential source of fibrinogen in the body."

Mann and Bollman,<sup>5</sup> however, were unable to demonstrate any consistent changes in the clot-forming elements of the blood in dogs following complete removal of the liver, but obtained a variation tending toward a decrease. They concluded "that the liver did exert considerable influence on the clot-forming elements of the blood, but that a number of other factors must also be considered." Mills<sup>6</sup> has isolated a tissue fibrinogen from many organs and tissues, and has utilized the preparation of fibrinogen from the lung as a

<sup>1</sup> Doyon and Kareff: *Compt. rend. Soc. de biol.*, 1904, **56**, 612, cited by Whipple and Hurwitz.

<sup>2</sup> Nolf: *Arch. internat. d. physiol.*, 1905, **58**, 30.

<sup>3</sup> Whipple, G. H. and Hurwitz, S. H.: *Fibrinogen of the Blood as Influenced by the Liver Necrosis of Chloroform Poisoning*, *Jour. Exper. Med.*, 1911, **13**, 137.

<sup>4</sup> Foster, D. P. and Whipple, G. H.: *Blood Fibrin Studies. IV. Fibrin Values Influenced by Cell Injury, Inflammation, Intoxication, Liver Injury and the Eck Fistula*, *Am. Jour. Physiol.*, 1921, **58**, 407.

<sup>5</sup> Mann and Bollman: *Loc. cit.*

<sup>6</sup> Mills, C. A.: *The Action of Tissue Extracts in the Coagulation of Blood*, *Jour. Biol. Chem.*, 1921, **46**, 167.

blood coagulant in clinical work. The relation of the liver, if any, to its origin as found in the lung cannot be determined accurately.

8. **Abnormal Function of the Liver.**—It can readily be seen that in case of hepatic disease, any one or all of the preceding functions might be impaired. There seems to be no doubt that some of these functions, including carbohydrate metabolism and the process of detoxification, are, to a certain extent, forced upon other organs when the liver is diseased. It is difficult to determine which function of the liver is affected first when it is diseased. However, it is very likely that the type of disease acts as the prime factor in determining which functions are impaired first. Mann and Bollman<sup>1</sup> feel that the destruction of uric acid is one of the first functions to be disturbed in disease of the liver. If the elimination of bilirubin is impaired, it will be retained, and, because of its toxicity, exert a poisonous influence on the other organs. Likewise, if the liver fails to remove the toxic products of digestion arriving through the portal vein, and the by-products of protein metabolism, serious damage will be inflicted elsewhere, and the formation of a vicious circle will be established.

It is possible that pathological conditions of the liver, in many cases stimulate the formation of gall stones in the gall bladder, as well as within the liver itself. This relationship has been discussed in the section on Formation of Gall Stones.

As Walters and Mayo<sup>2</sup> have remarked, if the liver is unable to supply glucose to the tissues because of depletion by such factors as muscular activity, postoperative shock, toxemias of pregnancy, etc., acidosis will likely result. In addition, if sufficient glucose is not available, the protein tissues of the body are broken down for the purpose of producing the necessary glucose, and the resultant excess nitrogenous material must be excreted in the urine as ammonia and urea. If the kidney is unable to excrete these products, because of disease or excess amount, uremia may develop.

### JAUNDICE.

**Bile Pigment Metabolism.**—Jaundice is produced by an accumulation of bilirubin, above its normal amount, in the blood. Normally bilirubin is present in the blood in a concentration varying from 1 in 1,000,000 to 1 in 500,000 (1 to 2 mg. per 1000 cc. serum). When this content is raised to 1 in 40,000 (25 mg. per 1000 cc. serum) or above, macroscopic or tissue jaundice results. The stage of hyperbili-

<sup>1</sup> Mann and Bollman: Loc. cit.

<sup>2</sup> Walters, W. and Mayo, W. J.: Abnormal Function of the Liver, *Jour. Am. Med. Assn.*, 1925, **85**, 883.

rubinemia below the amount necessary to produce visible jaundice is termed latent jaundice.

Sufficient data has accumulated to enable us to trace the entero-hepatic circulation of bile pigments. When the bilirubin enters the intestinal tract in the bile, it is converted into hydrobilirubin which is in turn converted into stercobilin and urobilinogen by the action of intestinal bacteria. Urobilin is an oxidation product of urobilinogen, is absorbed from the intestinal tract, enters the portal system and again takes a part in bilirubin formation.

As long ago as 1847, Virchow, observing the discoloration about hematomas, suggested the formation of bilirubin from hemoglobin and its relation to jaundice, but not until recent years was any proof offered. The experiments of Whipple and Hooper,<sup>1</sup> and Mann, Bollman and Magath<sup>2</sup> have demonstrated the origin of bilirubin in other organs besides the liver, namely, the spleen, bone-marrow and lymph nodes. They also noted an increase in bilirubin formation after the injection of hemoglobin. The latter group of authors noted that after removal of the liver, the plasma became tinged with bilirubin three to six hours after the operation. A yellow color was noticed in the scleræ of those animals living sixteen hours or more. This pigment developed even when all the abdominal viscera were removed. These experiments also substantiate the theory of elimination of bilirubin by the liver. It is difficult, however, to locate the *exact* source of the pigment. Mann and his associates remark that "it is possible that endothelial cells throughout the body have the ability to form bile pigments. The logical site for both the destruction of worn-out, functionless erythrocytes, and the disintegration of hemoglobin, would be at the point where the greatest functional stress is placed on the erythrocytes, in the capillaries."

Van den Bergh,<sup>3</sup> by utilizing the reaction of Ehrlich's diazo reagent to bile pigments, has been able to formulate the idea that there are two kinds of bilirubin. He suggests that a prompt direct reaction is obtained only from a bilirubin that has passed through the polygonal cells of the liver and subsequently has been absorbed because of obstruction. In case a delayed reaction is obtained, he suggests that the bilirubin had been formed independently of the liver and had not passed through the liver cells. Heyd, Killian and

<sup>1</sup> Whipple, G. H. and Hooper, C. W.: Icterus: A Rapid Change of Hemoglobin to Bile Pigment in the Circulation Outside the Liver, Jour. Exper. Med., 1913, **17**, 612.

<sup>2</sup> Mann, F. C., Bollman, J. L. and Magath, T. B.: Studies on Physiology of the Liver. IX. The Formation of Bile Pigment after Total Removal of the Liver, Am. Jour. Physiol., 1924, **69**, 393.

<sup>3</sup> Van den Bergh: La recherche de la bilirubine dans le plasma sanguin par la methode de la reaction diazoique, Presse med., 1921, **29**, 441.



Klemperer<sup>1</sup> offer as supportive evidence two clinical facts: (1) Bile in the gall bladder which has passed through the liver always gives a typical prompt direct reaction; (2) bilirubin obtained from serous fluids as in hemorrhagic effusions, etc., which is quite certainly elaborated independently of the polygonal cells of the liver, gives a delayed reaction or none at all. Heyd, Killian and Klemperer state further that "it is the cells in the reticulo-endothelial cell system, and particularly Kupffer's cells in the liver and reticular cells of the spleen which are concerned with the breaking down of hemoglobin into bilirubin." They agree with Aschoff<sup>2</sup> and others that the reticulo-endothelial cells of other organs including bone-marrow, lymph glands, etc., may be the seat of bilirubin formation. Minkowski and Naunyn<sup>3</sup> obtained conflicting data by finding no formation of bilirubin in the circulation when the liver had been removed from geese. The explanation of this probably lies in the assumption that the number of reticulo-endothelial cells in the various organs vary considerably in different species, and in the goose are contained almost entirely within the liver.

In the light of the foregoing experiments there seems little doubt that the cells of the reticulo-endothelial system take up by phagocytosis, intact red blood corpuscles, debris of corpuscles, and hemoglobin. The hemoglobin is broken down in these cells, and the iron-containing portion, hemosiderin, which can be demonstrated in them by staining methods, acts as a link in the chain toward the formation of bilirubin.

Rous and Drury<sup>4</sup> conclude that jaundice which develops after obstruction of the common duct in the absence of complications expresses the physiological wastage of corpuscles occurring from day to day; and the intensity of bilirubinemia varies as does the total of functioning hemoglobin-containing tissue from which this wastage takes place.

Snell<sup>5</sup> in some interesting experiments consisting of the injection of a sublethal dose of bile into animals intravenously, found that there was dye retention for a period of twenty-four hours. After twenty-four hours, the normal hepatic function of excretion of dyes was resumed. It is a well-known fact that bile salts and bile

<sup>1</sup> Heyd, C. G., Killian, J. A. and Klemperer, P.: Pathogenesis of Jaundice, Surg., Gynec. and Obst., 1927, **44**, 489.

<sup>2</sup> Aschoff, L.: Lectures on Pathology, New York, P. B. Hoeber, Inc., 1924, p. 365.

<sup>3</sup> Minkowski, O. and Naunyn, B.: Beiträge zur Path. der Leber und des Icterus, Arch. f. exper. Path. u. Pharmacol., 1886, **21**, 1.

<sup>4</sup> Rous, Peyton and Drury, D. R.: Jaundice as an Expression of the Physiological Wastage of Corpuscles, Jour. Exper. Med., 1925, **41**, 601.

<sup>5</sup> Snell, A. M.: The Clinical Application of Recent Studies on Jaundice, Surg., Gynec. and Obst., 1926, **42**, 528.

acids are hemolytic and therefore should result in an immediate formation of bilirubin far above normal limits. This calls for an increase in the excretory function of the liver in eliminating the bilirubin. It seems logical to assume that while the liver was burdened with the duty of eliminating the bilirubin, it would not excrete the dye in the normal time. However, it is probable that the bile salts and acids exerted a direct toxic effect on the liver cells, in addition to producing an excess amount of bilirubin for the liver to excrete.

It also seems probable that the cholagogic action of bile salts after ingestion by the human patient may partly be due to an increase in production of bilirubin, thereby requiring a larger amount of bile to eliminate the pigment.

It was originally supposed that the path of bile pigment in its production of jaundice took place through the lymphatics as well as through the hepatic vascular capillaries. Whipple and King,<sup>1</sup> however, found that the amount of bile pigment obtained from the thoracic duct in case of jaundice was so small that it was negligible. The experiments of Bloom,<sup>2</sup> however, quite conclusively demonstrate that in obstructive jaundice, considerable pigment passes into the lymphatics of the liver and main lymph trunks. After removal of the kidneys and gall bladder and ligation of the thoracic duct, as well as the common bile-duct, he was able to find bilirubin in the cisterna chyli, an hour or so after the ligation. As time elapsed, after ligation of the common bile-duct, larger amounts could be demonstrated in the lymph. The question arises that possibly the removal of the kidneys in Bloom's experiments was a factor in the conflicting results as compared to the findings of Whipple and King.

**Theories of Formation of Jaundice.**—Previous to the years 1910 and 1912, it was generally accepted that all forms of jaundice were due to obstruction, which occurred either in the larger bile-ducts or in the fine capillaries. Since that time, evidence has gradually accumulated to admit other possibilities of formation of icterus, which are similar to vague ideas expressed by Virchow in 1847. His theory lost favor for a time, only to be truthfully established in detail a few years ago.

McNee<sup>3</sup> has offered a theory of jaundice which has been quite

<sup>1</sup> Whipple, G. H. and King, J. H.: The Pathogenesis of Icterus, *Jour. Exper. Med.*, 1911, **13**, 115.

<sup>2</sup> Bloom, W.: The Rôle of the Lymphatics in the Absorption of Bile Pigment from the Liver in Early Obstructive Jaundice, *Bull. Johns Hopkins Hosp.*, 1923, **34**, 316.

<sup>3</sup> McNee, J. W.: Jaundice: A Review of Recent Work, *Quart. Jour. Med.*, 1923, **16**, 390.

widely accepted and explains the major points known about jaundice up to date. His points are as follows: "The theory of jaundice developed as a result of the recent investigations, has at its root, the view that the polygonal glandular cells of the liver are not essentially concerned with the manufacture of bile pigment, but have chiefly to do with its transference from the vascular capillaries into the bile capillaries. It seems probable, if this view is correct, that in passing through the polygonal cells, bilirubin is modified in some way and this is the explanation offered at present to account for the two varieties of bilirubin made evident by the van den Bergh test. The view is further put forward that it is the cells of the reticulo-endothelial system, either those in the spleen or the Kupffer cells of the liver, which deal with the breaking down of hemoglobin and the elaboration of bile pigment." This conception is based on animal experiments, in which, during blood destruction, bile pigment, and fragmented erythrocytes have been seen together in the endothelial cells of the liver, but have never been seen as such in the polygonal cells of the liver.

Working on this assumption, McNee offers a variety of ways that jaundice might arise: If bile pigment, formed in the endothelial cells, passes through the glandular cells to reach the bile capillaries, encounters obstruction as would be produced by duct obstruction, it would pass directly into the hepatic vein and accumulate in the circulation. In case of excessive blood destruction, which would be encountered in hemolytic jaundice, more bilirubin is formed by the reticulo-endothelial system than the polygonal cells can deal with. The excess will then spill over into the hepatic vein. If, in addition to damage of the polygonal cells, there is an obstruction in the bile passages, some bilirubin might pass directly into the hepatic vein, and some pass through the damaged polygonal cells, only to be obstructed in the bile passages and reabsorbed.

**Classification of Types of Jaundice.**—All the various types of jaundice can be classified into one of three main groups.

1. **Obstructive or Extra-hepatic Jaundice.**—Of the many causes of this type may be included (a) obstruction by foreign bodies within the ducts, as gall stones or parasites; (b) by pressure on the duct from without, as by tumors of the pancreas, stomach, etc.; (c) by stricture or obliteration of the duct; (d) by tumors growing within the orifice of the duct; (e) by inflammatory conditions in the duodenum (this is quite certainly a very rare cause of jaundice).

There can be no question that all cases of jaundice whether of the obstructive, toxic or infective type are injurious to the liver. In obstructive jaundice there is marked distention of the bile-ducts; the

bile capillaries are dilated and many ruptured. The entire liver is swollen and edematous and engorged with bile. The liver cells continue to secrete but soon are so badly damaged that the output of bile pigments, bile salts and bile acids is markedly decreased. Bile salts as well as bile pigments will be found in the urine.

2. **Toxic and Infective Jaundice.**—This type includes icterus in (a) catarrhal jaundice; (b) spirochetal icterus; (c) sepsis; (d) acute yellow atrophy; (e) pneumonia; (f) some cases of poisoning.

The mechanism of production of jaundice in this second type (toxic and infective) is uncertain. Naunyn<sup>1</sup> contends that cholangitis, or inflammatory changes in the bile passages are the basis of it. It seems probable, however, that both a damage to the liver cells, and obstruction in the bile passages from cholangitis, fluctuate in position of importance.

3. **Hemolytic Jaundice.**—In this group are included (a) primary anemias such as a pernicious anemia, splenic anemia or Banti's disease; (b) icterus neonatorum; (c) familial icterus; (d) "disassociated jaundice." French observers are largely responsible for the application of the term dissociated jaundice. It includes such conditions as those in which either the bilirubin or bile salt is retained and reabsorbed into the blood, while the other is being excreted in the normal way.

Hemolytic icterus is characterized mainly by a high bilirubin content of the blood, but generally with no appearance of pigment in the urine. In a case of hemolytic jaundice encountered by McNee,<sup>2</sup> in which he found a bilirubinemia of 11 units, he could detect no bilirubin in the urine. He states that "the threshold value of the kidney for the bilirubin in hemolytic jaundice is entirely different from that obtaining in the obstructive variety, and in fact it may be doubted if in true hemolytic jaundice, without some added complication, bilirubin ever passes through the kidney at all." This is a very important characteristic, especially from the standpoint of differential diagnosis between obstructive and hemolytic jaundice. The fact that the spleen is an important factor in the production of hemolytic jaundice is supported by the striking relief obtained in some cases by splenectomy. The jaundice depends on blood destruction in excess, brought about by over-activity of the cells of the reticulo-endothelial system, especially of the spleen. The excretory power of the liver in regard to bilirubin is for practical purposes normal in hemolytic jaundice. It is conceivable that due to demands made upon the liver cells by the increased formation of

<sup>1</sup> Naunyn, B.: *Mittel. aus dem Grenzgeb. der Med. und Chir.*, Jena, 1919, **31**, 537.

<sup>2</sup> McNee, J. W.: *Loc. cit.*



bilirubin elsewhere, sufficient hyperplasia might take place to create a more efficient excretory system than is normally present. Whether this over-activity results in or is dependent upon the increase in size of the spleen, which is seen so commonly, cannot definitely be determined. Following this excessive blood destruction, there is such a marked increase in the bilirubin content of the blood that the liver, even in its normal state cannot properly eliminate the pigment. Bile salts are secreted normally and are found in the stool. Tests for determination of liver function usually do not reveal much impairment.

Heyd, Killian and Klemperer<sup>1</sup> have devised a chart depicting the mechanism of the various types of jaundice in such a concise manner that it is given in detail below.



The symbols A and A' after the word "bilirubin" are used to designate the possibility of the existence of two kinds of bilirubin.

<sup>1</sup> Heyd, C. G., Killian, J. A. and Klemperer: Loc. cit.

**Relation of Bile Acids and Salts to Jaundice.**—The bile acids (glycocholic and taurocholic) which occur in the bile as their respective sodium salts are synthesized in the body only by the liver, and are a normal constituent of the bile. Probably the two most important functions of these salts are their fat-splitting ability and assistance in the protective mechanism by chemical combination with poisons such as alkaloids, etc.

If, through the mechanism of obstructive jaundice, the content of glycocholic and taurocholic acid in the blood become sufficiently high they act as severe poisons. A large part of their toxicity has been ascribed to their hemolytic action when present in the blood stream in excess. Small quantities stimulate the central end of the vagus, and large amounts influence the heart. When present in excess, as in obstructive jaundice, they are thought, therefore, to be responsible for the bradycardia, irregularity of pulse and fall in blood-pressure. The itching and irritation of the skin in obstructive jaundice is thought to be due to bile salts deposited therein, because of the absence of itching in hemolytic jaundice. The tendency toward spontaneous hemorrhages observed occasionally in jaundiced patients is assumed to depend partly upon injury to the capillary endothelium by the bile salts. The bile salts may be an important factor in the reduction in clotting-time in jaundice, but it is suggested by Lee and Vincent, as mentioned in Chapter VI, that it is due, at least in part, to a binding of the plasma calcium by bile pigment. However, Haessler and Stebbins<sup>1</sup> feel that the delayed coagulation may be due to the interference of bile salts with the conversion of fibrinogen to fibrin.

Croftan<sup>2</sup> has very thoroughly summarized the physiological effects of bile acids as follows: (1) A powerful cytolytic action affecting both blood corpuscles and tissue cells; (2) a distinct cholagogue action; (3) in small doses they aid coagulation; (4) in large doses they retard coagulation; (5) slow the heart action; (6) in small doses they act as vasodilators; (7) in large doses, as vasoconstrictors; (8) reduce motor and sensory irritability; (9) act on the higher cerebral centers, causing coma, stupor and death.

## BASIS AND RATIONALE OF TESTS OF LIVER FUNCTION.

The fact that the liver is the largest organ in the body implies that its functions, both numerical and quantitative, have a propor-

<sup>1</sup> Haessler, H. and Stebbins, M. G.: *Effect of Bile on the Clotting-time of Blood*, *Jour. Exper. Med.*, 1919, **29**, 445.

<sup>2</sup> Croftan, A.: *The Bile Acids as a Remedy*, *New York Med. Jour.*, 1906, **83**, 810.

tionate significance to the body as a whole. The known functions are many indeed, and the ones unknown at the present time undoubtedly total many more. It is this variability of function which is the seat of the difficulty in obtaining a single test which can be accepted as an indicator of disturbed liver function. However, this extreme importance of the organ justifies the utmost effort in obtaining more satisfactory hepatic tests, than we have at hand at the present time. It is logical to conclude that hepatic tests never will be as satisfactory as tests of renal function because of the inclusion of only one major function (excretory) by the kidney, with but few subsidiary duties. Mann has very aptly expressed the regret that many of the tests of hepatic function have very little physiological basis. However, the greatest drawbacks to most of these tests would seem to be a lack of required sensitivity, since practically all of them will disclose dysfunction of the organ, if the disease is sufficiently severe.

The difficulties encountered in standardization of experimental production of hepatic disease in animals equal, and probably exceed by far, the difficulties met clinically in establishing a diagnostic criterion which will coincide with the actual pathological condition and thereby offer a control for the particular hepatic test being used.

Many methods of experimentally producing liver impairment or disease, as a means of testing various procedures for determination of liver function, have been suggested. Perhaps the most commonly used method is the production of liver injury by the use of chloroform and phosphorus. A consistent amount of hepatic damage is difficult to produce in animals even by giving the same amount of chloroform per kilogram of body weight over a given length of time. The dye test (phenoltetraiodophthalein) bears out this inconsistency by yielding varied figures of retention. It is encouraging, however, to note that the animals which later succumbed, either because of the hepatic damage or complications, practically always showed a greater retention of dye even at the time when hepatic damage was first demonstrable, than the animals which survived the experimental procedures. To obtain a liver necrosis with chloroform it is necessary that the liver should be relatively poor in glycogen. The maximum damage is found about forty-eight or seventy-two hours after the chloroform anesthesia and then gradually decreases. After a few days no more damage can be found and the animal regains his previous health, if it has not succumbed. A moderate amount of hepatitis, cholangitis and cirrhosis can be produced by bacteria, but the extent of the pathology cannot be controlled. The opera-

tive production of an Eck's fistula assures one of a progressive atrophy, extending over several weeks, but again there is a great variability in the amount of damage sustained by the liver. Many of the animals will die before adequate experiments can be conducted. The diet must be carefully chosen lest too much protein is partaken.

Perhaps the most promising method of obtaining liver impairment is by operative removal according to the method of Mann and Magath.<sup>1</sup> They found that 70 per cent of the liver could be removed before the animal's life was seriously jeopardized. The ability of the liver to regenerate rapidly and to regain its loss of tissue, as demonstrated by Mann and Bollman has been mentioned elsewhere in this chapter.

The methods of experimentally producing liver insufficiency, as depicted in the preceding paragraphs, forces one to admit that sufficient similarity to diseases of the liver in man cannot be produced to allow of accurate comparison of various hepatic tests. Mann and Bollman<sup>2</sup> have devised a test of uric-acid tolerance, as previously mentioned, which seems almost specific for testing hepatic function in the dog, but which they believe would be difficult to apply to the human. In support of this assertion, Greene<sup>3</sup> remarks that "in the dog, the liver is directly concerned with the metabolism of uric acid which accumulates in the blood following hepatectomy; in man no noteworthy change in the amount of uric acid or other non-protein nitrogenous constituents of the blood has been observed in hepatic disease." He states further: "In the dog, urea formation ceases after the complete removal of the liver. In man a comparable degree of hepatic insufficiency is not observed, even with the grossest hepatic changes."

It can, therefore, be concluded from the foregoing remarks, that gross comparisons can be made between the liver functions of man and the dog, but from the standpoint of accuracy of detail considerable conflicting data are revealed. We are forced to assume then, that more accurate ideas regarding the merits of the various tests can be obtained from their clinical application than from animal experimentation, if care is exercised in diagnoses and estimation of pathological damage as determined at operation, etc.

<sup>1</sup> Mann, F. C. and Magath, T. B.: The Production of Chronic Liver Insufficiency, *Jour. Physiol.*, 1922, **59**, 485.

<sup>2</sup> Mann, F. C. and Bollman, J. L.: *Loc. cit.*

<sup>3</sup> Greene, C. H.: The Clinical Use of Tests for Hepatic Function, *Jour. Am. Med. Assn.*, 1925, **85**, 1476.



**FORMATION AND SIGNIFICANCE OF "WHITE BILE."**

In 1911, Kausch<sup>1</sup> suggested that "white bile" was a secretion of the mucosa of the biliary passages which occurred with obstruction when the secretion of the mucosa of these passages was greater than its resorption. In 1921 Rous and McMaster<sup>2</sup> proved the source to be the mucosal surface of the biliary passages by obtaining it experimentally from an obstructed duct which was deprived of its connection with the gall bladder. They showed further, that although an obstruction was produced in the common duct experimentally, no "white bile" could be obtained in the presence of a gall bladder which was performing its concentrating function in a normal manner, because of the mixing of the concentrated contents of the gall bladder. If, however, the cystic as well as the common duct was tied, the formation of "white bile" could be obtained routinely. During the first few days, following the ligations, the contents of the ducts retained their pigmented color, in fact became darker on account of the conversion of bilirubin to biliverdin. In a few days the pigment had become less in amount and by the tenth or eleventh day the contents of the ducts were colorless and devoid of cholates.

The production of "white bile" in the gall bladder is not so readily and consistently obtained following obstruction. Rous and McMaster found that within the first few days the contents turned a greenish-black, but as weeks elapsed it thickened to a tar or jelly. The viscosity is due to the mucous secretion of the gall bladder. The extent of persistence of concentrating ability by the gall bladder, in the presence of obstruction is difficult to determine, but authorities agree that the concentration of the contents, especially the pigments, does not take place more than a few days following the obstruction. As mentioned in the preceding paragraph, Rous and McMaster found that after production of obstruction, the change in color of the gall-bladder contents, from a brown to a much darker color (greenish-black) is due to oxidation of bilirubin to biliverdin. By quantitative methods and dilution tests they found that as time elapsed following the obstruction, the amount of bilirubin decreased until it was found to be practically absent after about five weeks. The biliverdin increased for a time but also gradually decreased as time elapsed. After forty-four days, which was the longest period

<sup>1</sup> Kausch, W.: *Der Hydrops des gesamten Gallensystems bei chronischem Cholechusverschluss und seine Bedeutung für den Chirurgen*, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1911, **23**, 138, quoted by Judd and Lyons.

<sup>2</sup> Rous, P. and McMaster, P. D.: *Physiological Causes for the Varied Character of Stasis Bile*, Jour. Exper. Med., 1921, **34**, 75.

studied after obstruction, they found the amount of pigment to be "not more than twice that of normal bile, instead of six to ten times the quantity as during the first ten days."

The presence of infection within the gall bladder apparently changes entirely the reaction in the presence of obstruction. Rous and McMaster remark that "infection may so change the gall bladder that a white system develops where a green is expected." In one of their animals chronic infection led to a thickening of the bladder wall, and the gall bladder as well as ducts were found distended with a colorless syrupy fluid, containing a few shreds of pus.

Rous and McMaster found "white bile" to have the following characteristics in the dog: It is slightly alkaline to litmus, clear, almost watery, practically devoid of cholesterol and of low specific gravity to judge from one specimen tested.

We have found, along with Mitchell and Stifel<sup>1</sup> and many others, that the secretory pressure of the liver in dogs, quite constantly is found to be between 250 and 300 mm. of bile. Mitchell and Stifel have also observed that after the first three hours, the pressure within the ducts varied by only a few millimeters from the original high level established. This observation would suggest that white bile is dependent upon secretory activity of the liver and that it will not be produced under a pressure much greater than the secretory pressure of the liver.

Although a few days after the production of obstruction, no biliary secretion is found to be draining into these ducts containing "white bile," it does not necessarily follow that the liver has ceased secreting. The path of the bile in case of duct obstruction, through the ruptured bile capillaries into the blood stream and lymphatics has been discussed elsewhere in this chapter. The resumption of the bile flow within a very few days after relief of the obstruction is quite presumptive evidence that the liver had not ceased secreting.

The method of escape of pigments from obstructed ducts is not agreed upon, except that it takes place in the liver. Heidenhain<sup>2</sup> and others believe that the place of escape is situated at the junction of the intralobular bile capillaries with the collecting channels of Glisson's capsule. This assumption, of course, does not explain the escape of the pigment from the gall bladder when the cystic duct is obstructed. The only avenue of escape in such a condition

<sup>1</sup> Mitchell, W. T. and Stifel, R. E.: The Pressure of Bile Secretion during Chronic Obstruction of the Common Bile-duct, *Bull. Johns Hopkins Hosp.*, 1916, 27, 78.

<sup>2</sup> Heidenhain, R.: Studien des physiologischen Instituts zu Breslau, *Leipsic*, 1868, No. 4, p. 234, quoted by Rous and McMaster.

would be a very slow absorption of pigment through the gall-bladder wall, with replacement by mucus.

McMaster and Rous<sup>1</sup> have ascribed the term hydrohepatosis to the presence of white bile in the ducts and remark upon the similarity to hydronephrosis. In each case the secretion or excretion takes place against a pressure obstacle and the total output is decreased.

It is commonly known that in cases of severe hepatic disease the output of bile becomes very pale and a few observers are of the opinion that a white bile can be produced by the liver if severely diseased. Drury and Rous<sup>2</sup> have demonstrated that in the presence of a severe liver damage produced by chloroform, a colorless bile is secreted. During the first twenty-four hours, the volume of bile and amount of pigment were found to be slightly lessened, and during the next twenty-four hours greatly diminished. If the injury was lethal the animals died on the second or third day. The fluid secreted during the period when the animals were moribund had none of the characteristics of bile, was colorless, cholesterol-free, and revealed no cholates on Hay's test. If the animal survived, the secretion on the third day increased in amount and contained more pigment. Within a few days the amount and character of the secretion had returned to normal.

White bile in the common duct is relatively infrequent but will be observed occasionally in patients having common-duct obstruction, especially those seen late in the disease. Judd and Lyons<sup>3</sup> encountered white bile 19 times in 649 operations on the common or hepatic duct at the Mayo Clinic. Of this number 361 were patients with stone in the common duct. In 9 of these cases white bile was encountered, or an occurrence of 2.4 per cent. The time necessary for the production of white bile in the human cannot be determined accurately but quite certainly is dependent upon whether the obstruction is complete or not. The shortest period of jaundice in the series reported by Judd and Lyons was two weeks. The presence of white bile in the common duct of one of their patients and light-green content in the gall bladder coincides with the appearance of white bile in the duct of animals, as reported by Rous and McMaster, before it occurs in the gall bladder. Judd and Lyons encountered a mortality of 21 per cent in their series. They have described a "liver shock," which they believe has been a result of allowing the escape of too much bile at one time in those cases in which a large

<sup>1</sup> McMaster, P. D. and Rous, P.: Hydrohepatosis, a Condition Analogous to Hydronephrosis, *Proc. Nat. Acad. Sci.*, 1923, 9, 19.

<sup>2</sup> Drury, D. R. and Rous, P.: Suppression of Bile as a Result of Impairment of Liver Function, *Jour. Exper. Med.*, 1925, 41, 611.

<sup>3</sup> Judd, E. S. and Lyons, J. H.: White Bile in the Common Duct, *Ann. Surg.*, 1923, 77, 281.

retention of bile was present in the distended ducts behind the stone. The bile in some of these cases was colorless, in others, tinged with pigment. They recommend the insertion of a tube into the cholechochous with a clamp attached so that the pressure can be relieved gradually during the first few days following operation.

To summarize: White bile is the product of the glands of the duct wall and is present macroscopically when the biliary secretion of the liver fails to get into the larger bile-ducts. It collects in the ducts only in the presence of a non-functioning gall bladder, except possibly in instances of long duration of obstruction. The mortality following operation is high and suggests the advisability of performing operations in these cases in two stages. Supportive measures such as glucose administration and blood transfusion should be resorted to.

## METHODS USED IN DETERMINATION OF LIVER FUNCTION.

The tests recommended for use in determination of liver function are so numerous and some of the tests so dependent upon certain functions of the liver, that an outline of the various methods is given below. A few of them apply perhaps to only one function. Others quite certainly offer information relative to many of the hepatic functions. Of this group we feel quite certain that the retention obtained by the dye test (in large doses) signifies impairment of more functions than any other single test. For the sake of convenience, each test is ascribed to the particular function of the liver, upon which it is most dependent

### I. Excretion of foreign products (dyes).

1. Phenoltetrachlorphthalein.
2. Phenoltetraiodophthalein.
3. Bromsulphalein.
4. Rose bengal.
5. Azorubin.
6. Indigo carmine.
7. Methylene blue.

### II. Tests dependent upon pigment metabolism.

1. Icterus index.
2. Van den Bergh.
3. Fouchet.
4. Urobilin.
5. Bilirubinuria.
6. Hemoglobin.
7. Injection of bilirubin.



## III. Carbohydrate tests.

1. Levulose tolerance.
2. Galactose.
3. Glucose.

## IV. Dependent upon disturbed nitrogen metabolism.

## V. Dependent upon power of detoxification.

1. Widal.
2. Conjugation tests.

## VI. Miscellaneous tests.

1. Bile salts in urine and blood.
2. Fragility of erythrocytes.
3. Blood coagulability.
4. Ferment tests.
5. Hemaconia test of Brulé.
6. Excretion of tetraiodophenolphthalein.

1. **Phenoltetrachlorphthalein.**—The work of Abel and Rowntree<sup>1</sup> in 1910, on the pharmacological action of some of the phthaleins and their derivatives showed that many of these were excreted in the bile, especially the tetra-halogen compounds. This has formed the basis of the extensive use to which some of them have been put, as a means of determining the functional capacity of the liver. In 1913 Rowntree, Hurwitz and Bloomfield<sup>2</sup> reported the use of phenoltetrachlorphthalein in a method of determining liver function. They recommended a dose of about 0.4 gm. and determined the amount of dye excreted in the feces quantitatively by colorimetric methods. This proved to be a cumbersome procedure and was later modified by McNeil<sup>3</sup> who introduced the improved technique of estimating the amount of dye excreted in the bile, which was obtained from the duodenum by means of a duodenal tube. A more accurate method was suggested by Rosenthal<sup>4</sup> who resorted to the estimation of the time and rate of disappearance of the dye from the blood stream after intravenous administration. This principle of determining the ability of the liver to remove dyes from the blood stream has been utilized subsequently in practically all the dye tests of liver

<sup>1</sup> Abel, J. J. and Rowntree, L. G.: On the Pharmacological Action of Some Phthaleins and their Derivatives, with Especial Reference to their Behavior as Purgatives, *Jour. Pharmacol. and Exper. Ther.*, 1910, **1**, 231.

<sup>2</sup> Rowntree, L. G., Hurwitz, S. H. and Bloomfield, A. L.: Experimental and Clinical Study of the Value of Phenoltetrachlorphthalein as a Test for Liver Function, *Bull. Johns Hopkins Hosp.*, 1913, **24**, 327.

<sup>3</sup> McNeil, H. L.: The Quantitative Estimation of Phenoltetrachlorphthalein Excreted in the Fresh Bile in Disease of the Liver, *Jour. Lab. and Clin. Med.*, 1916, **1**, 822.

<sup>4</sup> Rosenthal, S. M.: An Improved Method for Using Phenoltetrachlorphthalein as a Liver Function Test, *Jour. Pharmacol. and Exper. Ther.*, 1922, **19**, 385.

function and has been accepted as probably the most satisfactory. Obviously, before such a method can be considered of value, it must be demonstrated that the particular dye used is excreted by the normal liver in amounts exceeding 90 or 95 per cent. By this method the inaccuracy produced by loss of varying amounts of dye through other organs, is eradicated, and the time necessary for completion of a test is also shortened.

Rosenthal<sup>1</sup> recommends an intravenous dose of 5 mg. of phenoltetrachlorphthalein per kilo of body weight and the collection of blood samples fifteen minutes and one hour after the injection. More samples may be obtained if desired. He found that normally only 3 to 7 per cent remained in the blood fifteen minutes after the injection and that it was practically absent from the blood serum one hour after the injection. The liver of a dog is able to remove the dye from the blood stream within one-half hour following the injection of the dose of 5 mg. per kilo.

The injection of the dye should be performed under sterile precautions and the solution, which is obtained in a strength of 5 per cent, is slowly injected, taking care that none escapes outside the vein.

At the periods suggested (usually fifteen minutes and one hour after the injection) 5 or 6 cc. of blood are drawn from a vein in the opposite arm into a clean test-tube. The blood is centrifugalized and the serum pipetted into two small test-tubes. To the serum in one tube add a drop of 3 per cent hydrochloric acid and to the other tube add a drop of 5 per cent sodium hydroxide, which brings out the color of the dye. The alkalized serum is placed in a compartment of a suitable comparator box after the method of Walpole,<sup>2</sup> and the acidified serum which serves as a control, into an adjacent compartment. Behind the specimen, to which has been added alkali, place a tube of distilled water and in the compartment behind the tube containing the normal serum place a tube of standard. Select one which matches the color in the alkalized serum. If the color match falls between two standards, interpolation is necessary.

Standards may be made up by adding 10 mg. phenoltetrachlorphthalein to 100 cc. of water and making dilutions from this solution, which is considered 100 per cent. A small amount of alkali must be added to the water used in making the solutions and

<sup>1</sup> Rosenthal, S. M.: The Phenoltetrachlorphthalein Test for Hepatic Function, *Jour. Am. Med. Assn.*, 1924, **83**, 1049.

<sup>2</sup> Walpole, G. S.: Chart Presentation on Recent Work on Indicators, *Jour. Biol. Chem.*, 1911, **5**, 207.

dilutions to prevent fading. Such standards can be purchased if desired.

The amount of retention is considered to be a direct index of the amount of liver damage. Hemolyzed blood interferes considerably with the readings but this can partially be eliminated as suggested by Bloom and Rosenau,<sup>1</sup> by precipitating the hemolyzed blood with acetone. The extraction of the dye is not absolute but serves satisfactorily for ordinary purposes.

As Rowntree<sup>2</sup> and his associates remarked in their original article, the excretion of the dye in the urine is practically negligible in normal individuals. Greene, Snell and Walters note that rarely does the total output in the urine exceed 0.5 mg. and that the amount is apparently dependent on the concentration of the dye in the blood. The presence of 1 mg. or more in the urine is indicative of definite retention in the blood stream and signifies an impairment of hepatic function.

Rosenthal observed that for two or three days following the production of a common-duct obstruction in animals there was no retention of the dye after injection. Snell, Greene and Rowntree,<sup>3</sup> however, obtained a retention when the animals were observed for longer periods. The development of dye retention usually coincided with the first appearance of bile in the blood, which takes place about sixty hours after operation. Thereafter the amount of retention gradually increased, the maximum amount being obtained between the second and fourth week.

Bloom and Rosenau conducted some experiments on animals after removal of their liver and kidneys. In these animals the dye remained in the blood stream until death. After tying the cystic and common duct in normal animals the liver was able to remove large quantities. In no case of prolonged complete biliary obstruction did they obtain a retention greater than 4 per cent in the blood serum after one hour.

Rosenthal obtained the greatest retention in patients with arsphenamine or catarrhal jaundice, most of whom had a retention of 3 to 35 per cent after one hour. Patients having carcinoma of the liver revealed a retention of 12 to 20 per cent after one hour. The average of figures for patients with cirrhosis of the liver revealed only a mild retention of 6 to 20 per cent in one hour.

<sup>1</sup> Bloom, W. and Rosenau, W. H.: A Simple Method for the Determination of Phenoltetrachlorphthalein in Blood Serum, *Jour. Am. Med. Assn.*, 1924, **82**, 547.

<sup>2</sup> Rowntree, L. G., Hurwitz, S. H., and Bloomfield, A. L.: *Loc. cit.*

<sup>3</sup> Snell, A. M., Greene, C. H. and Rowntree, L. G.: Diseases of the Liver. II. Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, *Arch. Int. Med.*, 1925, **36**, 273.

Piersol and Bockus<sup>1</sup> reported normal figures of retention, 3 to 4 per cent fifteen minutes after the injection, in normal individuals. Five of 6 cases of syphilis receiving arsphenamine showed a mild retention following the dye. Likewise 5 of 7 patients having chronic gall-tract disease and 3 of 4 patients having diabetes showed a mild retention of the dye after injection.

Smith<sup>2</sup> conducted the Rowntree-Rosenthal test on 20 cases of normal pregnancy and 44 with toxemia. He found normal figures of below 7 per cent retention in fifteen minutes in the normal pregnant woman. One-half the patients with toxemia had a mild retention. This retention fell within two weeks following recovery from the toxemia. In the patients that succumbed to toxemia of pregnancy, lesions could be demonstrated in the liver, but Smith felt that there was not a very direct ratio of the amount of pathology to the amount of retention. Rosenfeld and Schneider<sup>3</sup> likewise obtained no retention in normal pregnant women and a slight retention in patients with toxemia. Krebs and Dieckman<sup>4</sup> observed a mild retention in patients suffering from toxemia of pregnancy.

Occasionally thrombosis results in the vein injected. Piersol and Bockus had 5 cases of thrombosis in 217 patients injected. Bloom and Rosenau had "37 per cent untoward reaction, including thrombosis, local reaction and chill."

**2. Phenoltetraiodophthalein.**—Our<sup>5</sup> chief reason for utilizing a substance which would stain the blood serum and still prove satisfactory for cholecystography was to obtain data on the excretory function of the liver. No special advantages other than its simultaneous use in cholecystography are claimed for phenoltetraiodophthalein, over any other phthalein dye used for determination of hepatic function, except that the larger dose (40 mg. per kilo of body weight), made necessary for cholecystographic purposes, increases its efficiency as a test of hepatic function. The chemical formulæ, staining properties, percentage of excretion by the liver and other characteristics of the various phenoltetrahalogenphthalein com-

<sup>1</sup> Piersol, G. M. and Bockus, H. L.: Comparative Studies in Liver Function by Some Later Methods, *Jour. Am. Med. Assn.*, 1924, **83**, 1043.

<sup>2</sup> Smith, J. A.: Phenoltetrachlorphthalein Test of Liver Function in Toxemias of Pregnancy, *Am. Jour. Obst. and Gynec.*, 1924, **8**, 298.

<sup>3</sup> Rosenfeld, H. H. and Schneider, E. F.: Improved Phenoltetrachlorphthalein Test for Liver Function in Pregnancy and its Toxemias, *Jour. Am. Med. Assn.*, 1923, **80**, 743.

<sup>4</sup> Krebs, O. and Dieckman, W. J.: Rosenthal Liver Function Test in Obstetrics, *Am. Jour. Obst. and Gynec.*, 1924, **7**, 89.

<sup>5</sup> Graham, E. A., Cole, W. H., Copher, G. H., and Moore, S.: Simultaneous Cholecystography and Tests of Hepatic and Renal Functions, *Jour. Am. Med. Assn.*, 1926, **86**, 467; Cholecystography: The Use of Phenoltetraiodophthalein, *Jour. Am. Med. Assn.*, 1926, **86**, 1899.

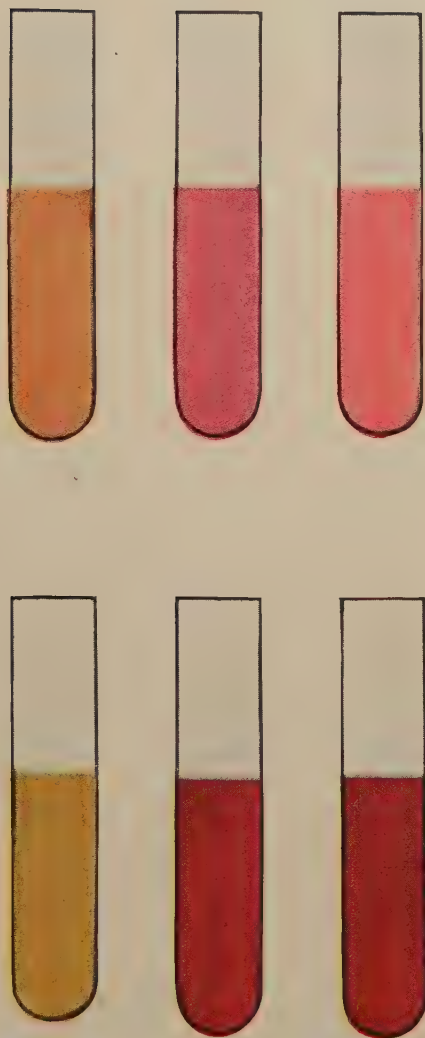


pounds are so similar that no particular one presents much advantage over any of the others, so far as estimation of liver function is concerned. We do feel, however, that the large dose is a very decided advantage, because by comparison with other organisms or mechanisms, an estimation of mild disturbances in function cannot be made by imposing a small load on that mechanism. It seems just as reasonable to assume the necessity of imposing a large amount of work upon a physiological process in the human to detect a slight impairment of function, as it would be, to detect a minor defect in any inanimate machine. Mann and Bollman have realized the importance of using large doses of dye (phenoltetrachlorophthalein) and remarked that they had to increase the dose considerably to obtain any evidence of retention in animals whose livers had been damaged experimentally.

Utilizing this increased dose we were able to detect a retention of the dye in the blood stream of animals whose livers had been previously damaged with chloroform in many cases when other tests revealed normal excretory time. Furthermore, phenoltetraiodophthalein revealed a retention above normal in practically every case where any of the other tests revealed retention.

*Technique of Administration.*—The chemical properties and technique of administration have been discussed in Chapter VII the section on Technique of Administration, and will be related only briefly here. A solution of the dye is made with freshly distilled water in a ratio of 2.5 gm. phenoltetraiodophthalein to 30 or more cubic centimeters of water (8 per cent solution or less), filtered, and sterilized in a water-bath for fifteen minutes. The dose is 40 mg. per kilogram of body weight but need not exceed 2.5 gm. and is given intravenously, preferably in the morning, on an empty stomach. The necessity of extreme care in thoroughly washing with saline, all the utensils used in the injection is again emphasized. *Extreme care must be utilized in washing the utensils (especially the medicine glasses into which the dye is transferred) free from lysol which drains into them from the sterile instrument used in handling them.* A control specimen of 7 or 8 cc. of blood may be taken before the dye is injected. It is advisable to inject a few cubic centimeters of saline solution (0.9 per cent) through the needle before injection of the dye to verify the position of the needle within the vein. The solution may be injected with a syringe or by gravity method. The time consumed in the injection should be at least five minutes. Before withdrawing the needle it is quite necessary to wash out the needle and vein with saline solution to minimize the possibility of thrombo-

## PLATE VI



### Color Reaction in Phenoltetraiodo Test of Hepatic Function.

Upper set of tubes illustrate the color reaction in the serum of a patient with a normal liver, after the intravenous injection of 40 mg. phenoltetraiodophthalein per kilo of body weight. First tube: serum before injection. Retention of 14 per cent—within normal limits. Second tube: alkalinized serum one-half hour after injection. Retention of 5 per cent—within normal limits. Third tube: alkalinized serum one hour after injection. Retention of 5 per cent—within normal limits. The lower set of tubes illustrate the color reaction in the serum of a patient with jaundice and moderate amount of hepatitis, after the intravenous injection of 40 mg. phenoltetraiodophthalein per kilo. First tube: serum before injection. Note the staining with bilirubin. Second tube: alkalinized serum thirty minutes after injection. Retention of 40 per cent of dye—considerably above normal. Third tube: alkalinized serum sixty minutes after injection. Retention of 20 per cent—also above normal.



sis of the vein. A sample of blood (about 12 cc.) is collected one-half hour and preferably again one hour after injection of the dye. It is advisable to obtain these specimens from a vein in the opposite arm if possible. The blood is allowed to clot, is centrifugalized, and the serum transferred to two clean tubes, the same size as the tubes containing the standard. The serum in one of these tubes is used as the control serum, instead of using serum obtained from blood collected before injection of the dye. This eliminates any error which might arise from a difference in the color (produced by hemolysis, etc.) of sera collected at different intervals. Using this technique, the arrangement of the tubes in the comparator box is as follows: In one hole of the box is placed one tube of the serum obtained from the half-hour sample of blood. We do not find the addition of dilute acid to this tube very helpful. Beside it is placed a tube containing distilled water. In front of the tube of water is placed the other half of the serum obtained from the half-hour sample, and a small drop of 10 per cent sodium hydroxide added to bring out the color. Mix well by shaking. In front of the tube of unalkalinized serum, place various standards until one is found which matches the color reflected through the tube of water and alkalinized serum. Care must be used in adding alkali to the tube of serum, as mentioned in the preceding paragraph, in order to obtain the maximum color. If too little alkali is added, the color will fade rapidly. If too much is added, the purple-red color turns brownish. For this reason, it is important to make the readings immediately after adding alkali to the serum. If the correct amount of alkali is added, the maximum color, which is obtained, will retain its intensity for hours. Usually, a small drop of 10 per cent sodium hydroxide is sufficient for 3 cc. of serum.

Hemolysis is undesirable, but since the same amount is present in the serum on each side of the box, a moderate amount does not jeopardize the results. If desired, the hemolyzed blood can be removed by acetone as suggested by Bloom and Rosenau. It has been found that comparisons of color are more easily made than the comparisons in other dye methods because of the *greater intensity of color which is produced by the large dose*. The colors are shown in the accompanying plate. (Plate VI.)

*Preparation of Standards.*—If 48 mg. of phenoltetraiodophthalein are added to 100 cc. of distilled water, the resultant solution will equal the 100 per cent standard and will represent the concentration of the dye in the blood stream after injection, before any of it is



excreted or conjugated by the liver. The formula used in estimating this amount of dye (48 mg.) to use in the standard is as follows:

$$\frac{\text{Dose per kilo} \times 100}{83.3^1} = \text{mg. per 100 cc. for 100 per cent standard.}$$

To prevent fading of the standards add 2 cc. of 10 per cent sodium hydroxide to every 100 cc. of water used in the preparation of the solution of the dye and also in the water used in making the dilutions. About 10 dilutions should be made between 5 and 100 per cent (*e. g.*, 5, 10, 15, 20, 25, 30, 40, 60 and 80 per cent). These tubes should be sealed tightly and *always kept in the dark when not in use*. They will keep for several months without fading, if kept in the dark when not in use. A retention of 10 to 12 per cent or less, thirty minutes after the injection, and 5 per cent or less, sixty minutes after injection are within normal limits for the human.

Comparisons were made in dogs, with phenoltetrachlorphthalein and bromsulphalein. On the third day following chloroform anesthesia a determination was made with phenoltetraiodophthalein and phenoltetrachlorphthalein, taking care to allow at least eight to nine hours to elapse between injections to prevent any residue of dye at the time of the next injection. On the fourth day following chloroform anesthesia, the injections were repeated but in reverse order. A comparison was also made between phenoltetraiodophthalein and bromsulphalein in a similar manner. Due to a faster elimination time by the liver in animals, the time for collection of specimens had to be shortened. There was a close similarity in the data obtained from each of the dyes. Occasionally phenoltetraiodophthalein would show a retention in the presence of normal figures obtained by the other two dyes. This increase in sensitivity was attributed chiefly to the increased dose rather than to any significant difference in the manner of excretion of the dyes. The bromsulphalein revealed a slightly greater sensitivity than the phenoltetrachlorphthalein.

The most important information, from the clinical standpoint, which we have derived from the excretion figures has been the poor status of operative risk in patients showing high retention. Another feature of importance which has revealed itself has been the aid in differential diagnosis between jaundice due to stone in the common duct and that due to carcinoma of the liver or pancreas. For details of clinical results see p. 392.

<sup>1</sup> The constant 83.3 represents the volume of blood in cubic centimeters per kilo of body weight. It is computed by using the ratio 1 to 12 for estimating blood volume as is recognized by Erlanger and others.

3. **Bromsulphalein.**—In an attempt to obtain a dye which would fulfill as many ideal qualities as possible for use in determination of hepatic function, Rosenthal and White<sup>1</sup> conducted experiments on several groups of dyes: (1) Phenoltetrahalogenphthaleins; (2) phenoltetrahalogenphthalein sodium sulphonate, including bromsulphalein; (3) tetrahalogenphenolphthalein; (4) halogen compounds of fluorescein. They employed rabbits in their experiments on the rate and the amount of biliary excretion and produced permanent biliary fistulæ by doubly ligating the common duct and tying a rubber catheter into the gall bladder. Injections were made into an ear vein and blood obtained from an external jugular vein by a small incision. Of this group of dyes they chose bromsulphalein (phenoltetrabromphthalein sodium sulphonate) as being the most suitable one for determining the excretory power of the liver because of a slightly faster rate of disappearance from the blood stream and a higher rate of retention following damage to the liver (by partial removal) in rabbits.

In a clinical report later Rosenthal and White<sup>2</sup> recommend the use of bromsulphalein for the reasons stated in the preceding paragraph and also because they had obtained none of the reactions such as thrombosis, etc., which occasionally resulted from the phenolte-trachlorphthalein injections. They concluded that a dose of 2 mg. per kilo was sufficient in the human. The dye is given slowly intravenously, as a 5 per cent solution in distilled water and 5 cc. of blood removed, preferably from the opposite arm, in five and thirty minutes. The blood is centrifugalized and the serum removed to two small tubes with a pipette. To one tube is added 2 drops of a 10 per cent solution of sodium hydroxide to bring out the color. A drop of 0.5 per cent hydrochloric acid is added to the other tube to clarify the solution. It is used as a normal serum. The amount of retention is determined by comparing the stained serum to standard solutions in the same manner as described under phenolte-trachlorphthalein.

The standards are made by adding 4 mg. of bromsulphalein to 100 cc. of distilled water and using this solution as the 100 per cent solution. All the water used in the solution and dilution must be alkalized by the addition of 0.25 cc. of 10 per cent sodium hydroxide to each 100 cc. of water. About 10 dilutions are made, ranging from

<sup>1</sup> Rosenthal, S. M. and White, E. C.: Studies in Hepatic Function, *Jour. Pharmacol. and Exper. Ther.*, 1925, **24**, 265.

<sup>2</sup> Rosenthal, S. M. and White, E. C.: Clinical Application of the Bromsulphalein Test for Hepatic Function, *Jour. Am. Med. Assn.*, 1925, **84**, 1112.

5 to 100 per cent. The tubes containing the standard solutions should be sealed and kept in the dark to prevent fading.

In patients with presumably normal livers, Rosenthal and White found a retention of 20 to 50 per cent of the dye in the serum five minutes after the injection. The average was 35 per cent. Thirty minutes after the injection the serum was found to be free from dye, or a very faint trace left. In normal individuals the dye occurred in the urine in negligible amounts, ranging from none at all to 0.5 per cent of the quantity injected.

In a series of 20 patients having liver disease, retentions varying from 3 to 99 per cent in one-half hour, were found. The higher figures were found in patients having obstructive jaundice, catarrhal jaundice and terminal stages of carcinoma of the liver. Lower figures between 17 and 22 were obtained in atrophic cirrhosis. A case of luetic cirrhosis gave the lowest amount of retention, 3 per cent.

In a report of the use of bromsulphalein, Bulmer<sup>1</sup> agrees that in doses of 2 mg. per kilo it is non-irritant and innocuous. He found a marked retention, however, varying from 5 to 45 per cent in normal persons thirty minutes after injection. These normals were recruited from the resident staff of the hospital and no explanation could be offered for the high retention which he found.

Bulmer also found the greatest retentions in patients with common-duct obstruction, either by stone or carcinoma of the pancreas. Patients having splenic anemia, leukemia, cardiac decompensation, diabetes, carcinoma of the stomach, pernicious anemia and several other diseases showed a mild retention ranging from 10 to 30 per cent. In fact he encountered very few instances in which the dye had disappeared within the allotted time of thirty minutes. In conclusion Bulmer states that "20 per cent of the cases give results which are obviously not representative of the degree of liver efficiency; the rest are acceptable." It should be stated, however, that the inconsistency of results as obtained by Bulmer in normal individuals has not been obtained by Rosenthal.

**4. Rose-bengal Test.**—In 1923 Delprat<sup>2</sup> reported the experimental use of rose bengal (diiodotetrachlorfluorescein) of the triphenyl-methane series, as a dye to test the excretion of the liver. He found its biliary excretion in the dog to be 6 per cent in one hour, 23 per cent in two hours and 43 per cent in five hours. None was found

<sup>1</sup> Bulmer, E.: The Bromsulphalein Test of Liver Function, *Quart. Jour. Med.*, 1927, **25**, 101.

<sup>2</sup> Delprat, G. D.: Studies on Liver Function; Rose-bengal Elimination from the Blood as Influenced by Liver Injury, *Arch. Int. Med.*, 1923, **32**, 401.

in the urine. Rosenthal and White<sup>1</sup> found a rapid removal of rose bengal from the blood after liver ligation which they interpreted as indicating that it was taken up by other tissues under these circumstances. Schmidt and Norman<sup>2</sup> report that under the influence of direct sunlight the dye readily hemolyzes erythrocytes *in vitro*, but Epstein, Delprat and Kerr<sup>3</sup> feel quite certain that this does not occur within the human body. Delprat found that the dye disappeared from the blood stream of the dog in eight to twelve minutes, but continued to appear in the bile for several hours after the injection. This excretion is similar to phenoltetrachlorophthalein. Definite delay was found in the excretion of rose bengal after the liver had been injured with chloroform.

In their clinical report, Epstein, Delprat and Kerr, recommend an intravenous injection of 10 cc. of a 1 per cent solution of rose bengal (100 mg.) in physiological sodium chloride solution as the dose after the injection. The needle is washed slowly with 5 to 10 cc. of salt solution and left in the vein. Exactly two minutes after injection of the dye, 10 cc. of blood are withdrawn from the needle and put into a centrifuge tube containing a few crystals of potassium oxalate. At eight and sixteen minutes, samples of blood are collected in a similar manner. The blood samples are then centrifugalized at 2000 revolutions per minute for thirty minutes. The blood should be handled carefully to prevent hemolysis. They have modified their original technic by substituting the use of artificial standards with a Hellige colorimeter and using the two-minute sample as a 100 per cent standard. The small amount lost in the tissues during the two-minute period is not considered significant, since the rate of excretion is a more reliable estimation of the excretory power of the liver. By setting the standard at 100, the amount of retention of dye in eight and sixteen minutes can be obtained in a direct ratio, by comparing with the 100 per cent or two-minute standard.

They found that in normal individuals only 42 to 52.5 per cent remained in the circulation at the end of eight minutes. At the end of sixteen minutes 23 to 26 per cent remained. In cases of chronic cholecystitis the elimination was usually within normal limits. With patients having obstructive jaundice, catarrhal icterus, acute infections of the liver and arsphenamine jaundice, the delay

<sup>1</sup> Rosenthal, S. M., and White, E. C.: Studies in Hepatic Function, Jour. Pharm. and Exp. Therap., 1925, **24**, 265.

<sup>2</sup> Schmidt, C. L. and Norman, G. F.: Protection Afforded to Red Cells against Hemolysis by Eosin, Jour. Infec. Dis., 1920, **27**, 40.

<sup>3</sup> Epstein, N. U., Delprat, G. D. and Kerr, W. J.: The Rose-bengal Test for Liver Function, Jour. Am. Med. Assn., 1927, **88**, 1619.



was very definite, being greatest in obstructive jaundice. Cases of cirrhosis showed moderate retention. Variable results were obtained with malignancy of the liver. In chronic cholecystitis, cardiac failure with congestion of the liver and tuberculous peritonitis, the figures were within normal limits.

A possible chance for error in the test suggests itself to us in the fact that the needles are left in position in the vein. In view of the frequent occurrence of collapse of the vein around the needle during withdrawal of blood it seems likely that there might be an impairment of flow of blood through the vein around the needle. The number of diseases with probable liver disease which show a retention with the rose-bengal test seems smaller than the number obtained by many other tests. Obviously, this lack of sensitivity, if it really is such, could probably be eradicated by increasing the dose.

**5. Azorubin Test.**—The principle of the azorubin test as introduced by Tada and Nakashimia<sup>1</sup> is the determination of the time of its appearance in the bile after the intravenous injection of 4 cc. of a 1 per cent solution. The duodenal tube is inserted and a flow of yellow bile obtained before the injection of the dye. Normally the bile becomes stained a deep red about forty minutes after the injection. In patients with hepatic disease the time of appearance of the dye in the bile is delayed. In acute catarrhal jaundice, Zinny<sup>2</sup> found that the rate of discharge paralleled the course of the disease. In three cases of chronic jaundice, no dye was discharged. In patients having gall-stone colic, the excretion diminished, but became normal after cholecystectomy. About 5 per cent of the dye appears in the urine. Fenstermann<sup>3</sup> has conducted tests on the excretion in the urine and found that a larger amount of dye is excreted by the kidneys in patients with hepatic disease.

**6. Indigo Carmine Test.**—Einhorn and Laporte<sup>4</sup> have utilized indigo carmine as an index of the excretory power of the liver. They give 10 cc. of a 1 per cent solution intramuscularly and determine the time of appearance in the bile by means of the duodenal tube. Normally the dye appears in the bile in thirty minutes. If

<sup>1</sup> Tada, Y. and Nakashimia, K.: New Dye for Test of Liver and Biliary Tract Function with Especial Reference to its Clinical Use, *Jour. Am. Med. Assn.*, 1924, **83**, 292.

<sup>2</sup> Zinny, M.: Study of Hepatic Function, Especially with Azorubin, *Prenza méd. Argent.*, 1926, **13**, 665.

<sup>3</sup> Fenstermann, R.: Liver Function Tests with Azorubin, *Münch. med. Wehnschr.*, 1926, **73**, 859.

<sup>4</sup> Einhorn, M. and Laporte, G. L.: Indigo Carmine as a Functional Permeability Test of the Liver, *New York Med. Jour.*, 1923, **118**, 350.

there is hepatic disease, the time required for appearance of the dye is lengthened.

**7. Methylene-blue Test.**—Cohn<sup>1</sup> tried the oral administration of 0.002 gm. methylene blue according to the method of Roch, but was unable to obtain satisfactory results.

**Pigmentary Tests.**—1. **Icterus Index.**—The estimation of bile pigment in the blood and its clinical application was first introduced by Blankenhorn<sup>2</sup> and Meulengracht.<sup>3</sup> The original work was done on blood plasma. On account of a slight opalescent color in the plasma caused presumably by platelets, Gram<sup>4</sup> introduced the use of serum instead of plasma. The term icterus index was adopted by Maue and Peter<sup>5</sup> and by Stetten<sup>6</sup> and has survived as an accurate label of the principles of the test. As far as is known, the yellow color of the blood serum is due only to bilirubin except for a slight change in color which has been observed following the ingestion of certain foods.

The technique of the test as modified and followed by Bernheim<sup>7</sup> consists of a comparison of the amount of pigment in the blood serum with the color of an arbitrary standard, by means of a colorimeter. Four or 5 cc. of blood are withdrawn from a vein, the blood allowed to clot and subsequently centrifugalized. The serum is removed with a pipette and compared with the standard solution of 1 to 10,000 potassium dichromate (0.05 gm. to 500 cc. distilled water). This solution is slightly paler than normal serum. Bernheim prefers the use of a Bock-Benedict colorimeter which requires less serum than the Duboscq type. The standard solution is put into a 15 mm. cell and the reading taken at the point on the scale when the serum and standard match. The standard number, 15, is then divided by the scale reading. The quotient is the icterus index. If the color of the serum is too deep it must be diluted with 0.9 per cent sodium chloride solution. The quotient is then multiplied by the number of dilutions.

<sup>1</sup> Cohn, H. M.: Liver Function Test with Methylene Blue, *Klin. Wchnschr.*, 1922, **50**, 2522.

<sup>2</sup> Blankenhorn, M. A.: The Bile Content of the Blood in Pernicious Anemia, *Arch. Int. Med.*, 1917, **19**, 344.

<sup>3</sup> Meulengracht, E.: Die klinische Bedeutung der Untersuchung auf Gallenfarbstoff in Blutserum, *Deutsch. Arch. f. klin. Med.*, 1920, **132**, 285.

<sup>4</sup> Gram, H. C.: Test for Pigment in Blood Plasma, *Ugesk. f. Laeger*, 1920, **82**, 1137.

<sup>5</sup> Maue, H. and Peter, A. B.: The Icterus Index of the Blood Serum, *Surg., Gynec. and Obst.*, 1922, **34**, 752.

<sup>6</sup> Stetten, DeWitt: The Surgical Value of the Estimation of the Bile Pigmentation (Icterus Index) of the Blood Serum, *Ann. Surg.*, 1922, **76**, 191.

<sup>7</sup> Bernheim, A.: The Icterus Index (A Quantitative Estimation of Bilirubinemia), *Jour. Am. Med. Assn.*, 1924, **82**, 291.

To obviate the necessity of venipuncture, Davis<sup>1</sup> has devised a method of making determinations with a few drops of blood, which are collected in capillary tubes after puncture of the end of the finger. The blood is allowed to clot in one of these capillary tubes, which measures about 10 cm. in length and 2 or 3 mm. in diameter. The end of the tube is sealed and the tube then centrifugalized to separate the serum. The serum is then matched with standards, using daylight and not artificial light. He uses Meulengracht's original standard of 1 to 10,000 potassium dichromate to represent an index of 1. Ten standards are made in concentrations varying between 1 to 10,000 and 100 to 10,000 and a small amount of each sealed in a capillary tube. A disadvantage of this test lies in the fact that the index figure obtained from a given sample of serum does not correspond to the figure obtained by the colorimetric test although variations can be detected satisfactorily. Hemolysis, or cloudy serum due to products of digestion interfere with the test.

The lowest index encountered by Bernheim was 2.3 and the highest 150. Authorities agree that the normal index is close to 5. The zone of latent jaundice lies between 5 and 15. When the index reaches 15 or 16, macroscopic jaundice will quite consistently be found.

This test is very accurate in ascertaining the amount of jaundice and detecting slight variations in the extent of icterus. Its greatest value probably lies in the application to the fluctuations of depth of jaundice. It is frequently of great value in the differential diagnosis of lesions presenting symptoms in the right upper quadrant, especially those of the acute type. Patients having cholecystitis or cholelithiasis frequently show an elevated index and still present no macroscopic jaundice. This of course would tend to rule out the possibility of renal disease which does not produce an elevation of the icterus index. However, many patients with cholecystitis and cholelithiasis are encountered, who do not show an increase in the index.

Extremely low figures (extending as low as 2.4) are obtained in secondary anemias including those of carcinoma, etc. This would suggest that the anemia which is present in malignant disease is not of hemolytic origin due to destruction of erythrocytes by the toxins. On the other hand the serum of patients with primary anemias including pernicious anemia, reveal a definitely increased index ranging from 6 to 13. It is agreed that this ability to differentiate

<sup>1</sup> Davis, D.: Icterus Index with Capillary Blood, *Am. Jour. Med. Sci.*, 1926, 172, 848.

primary from secondary anemias is quite consistent and is of much value.

Shattuck, Browne and Preston<sup>1</sup> have found the test very useful in determining the tolerance of the liver to arsenicals in the treatment of syphilis. They also have used it to advantage in determining whether obstructive jaundice had been relieved by operation.

An interesting but unexplainable observation has been recorded by Bernheim,<sup>2</sup> who found a relation between the blood-sugar tolerance and the icterus index. In diabetes, she found a high index during fasting and a decreasing index as the blood sugar rose. In normal persons, a normal index was obtained in the fasting state but an increasing index as the blood sugar rose.

It must be remembered that the icterus index test serves primarily as a detector of changes in the bilirubin content of the blood (whether produced by duct obstruction, hemolytic processes, or hepatic impairment), and only in the minority of cases as a test for disease of the liver. It is well known that a hyperbilirubinemia can exist and is in fact frequently found in the presence of a normally functioning liver.

**2. Van den Bergh Test.**—This is a qualitative and quantitative test of bile pigment in the blood as is the icterus index, but in addition, has the ability to differentiate two types of bilirubinemia. The method which was originally described by van den Bergh,<sup>3</sup> uses as its basic principle, the diazo reaction which was discovered by Ehrlich in 1884. Ehrlich found that if a small amount of a diazonium salt in acid solution be added to an alcoholic solution of bilirubin, coupling occurred with the development of an azo dye, azo-bilirubin.

*Technique.*—This is described so concisely and completely by Hall<sup>4</sup> that we shall give the actual technique almost *verbatim* according to his interpretation: Draw 5 cc. of blood by venipuncture into a dry centrifuge tube and allow to clot. Centrifugalize and remove the serum with a pipette. The diazo reagent which must be made up just before use is a mixture of two solutions.

<sup>1</sup> Shattuck, H. F., Browne, J. C. and Preston, M.: Clinical Value of Some Recent Tests for Liver Function, *Am. Jour. Med. Sci.*, 1925, **170**, 511.

<sup>2</sup> Bernheim, A.: *Loc. cit.*

<sup>3</sup> Van den Bergh, A. A. H.: *Der Gallenfarbstoff im Blute*, Leiden, S. C. Van Doesburgh, VIII, 1918; *La recherche de la bilirubine dans le plasma sanguin par la methode de la reaction diazoique*, *Presse med.*, 1921, **29**, 441.

<sup>4</sup> Hall, W. W.: Useful Hepatic Function Tests, *U. S. Naval Med. Bull.*, 1926, **24**, 843; The van den Bergh Reaction for Serum Bilirubin with Notes on Interpretation and Technic, *Jour. Lab. and Clin. Med.*, 1927, **12**, 529.



## Diazo reagent:

<i>Solution A.</i> <sup>1</sup>		
Sulphanilic acid . . . . .		1.0 gm.
Concentrated hydrochloric acid . . . . .		15.0 cc.
Distilled water . . . . .	q. s. ad.	1000.0 cc.

<i>Solution B.</i>		
Sodium nitrite . . . . .		0.5 gm.
Distilled water . . . . .		100.0 cc.

<i>To prepare fresh reagent.</i>		
Solution A . . . . .		25.00 cc.
Solution B . . . . .		0.75 cc.

*Qualitative or Direct Reaction.*—Place 0.25 cc. serum in each of 3 small test-tubes. To tube No. 1, add 0.2 cc. water. To tube No. 3, add 0.2 cc. freshly prepared diazo reagent. After waiting five minutes for reaction to become complete in control tube No. 3, add 0.2 cc. diazo agent to tube No. 2. Watch and time development of reaction. Prompt or immediate reaction begins before thirty seconds have elapsed. Comparison with serum control, tube No. 1, and completed reaction control, tube No. 3, will aid in detection of color.

One of four results may be obtained: (1) Prompt or immediate direct reaction. The color change begins immediately and reaches its maximum in two or three minutes. The color is a reddish-violet, whose intensity depends on the amount of bilirubin present. This type of reaction is obtained in cases of obstructive jaundice. (2) Delayed reaction. This begins only after one to thirty minutes and consists in the development of a reddish coloration, which deepens and becomes more violet. Either this type of reaction or a negative reaction is characteristically found in hemolytic jaundice. The indirect test should be performed in the face of a delayed reaction since either a delayed or negative result may be obtained in normal sera. (3) Negative reaction. This consists of the production of a pink color or no color whatever. Occasionally in normal individuals, but more frequently in patients with secondary anemia, no color change is noted after the addition of the diazo reagent. (4) Biphasic direct reaction. This term is used to designate reactions which begin within the thirty-second period, but whose color does not attain its maximum intensity until some time later (maybe as long as one hour). Hall is inclined to drop the term biphasic, since practically no sera attain their maximum color within thirty seconds. He defines a prompt reaction as one begin-

<sup>1</sup> All reagents must be reasonably fresh.

ning within thirty seconds after addition of the reagent, and a delayed reaction as one beginning slowly after thirty seconds and reaching its maximum very slowly, sometimes taking thirty minutes or longer.

*Quantitative Test or Indirect Reaction.*—To 1 cc. serum in a 15 cc. graduated centrifuge tube add 0.5 cc. diazo reagent. After a minute or two add 2.5 cc. 95 per cent alcohol and 1 cc. saturated solution of ammonium sulphate. Mix well with a stirring rod after each addition and finally centrifugalize.

The diazo reagent is added before the alcohol to allow coupling to take place. By this method very little, if any, bilirubin is carried down with the precipitated protein, as the azobilirubin is very soluble in alcohol while bilirubin is less so and is carried down with the precipitate in relatively large amounts if the reagents are added in the reverse order. The color of the supernatant fluid will vary from a faint pink color as in normal serum to a deep violet, depending on the amount of bilirubin present. The quantity of supernatant fluid is read on the graduations of the centrifuge tube and the dilution of the bilirubin contained in the cubic centimeters of serum used is thus directly obtained. The quantity of bilirubin present in the serum is now, as azobilirubin, entirely in alcoholic solution. This supernatant alcohol usually varies from 2.5 to 3 cc. As the color of the standard represents a bilirubin concentration of 5 mg. per liter, the calculation is:

$$\frac{\text{Standard}}{\text{Unknown}} \times \text{Dilution of unknown}^1 \times 5 = \text{mg. bilirubin per liter of serum (with plunger colorimeter)}$$

$$\frac{\text{Unknown}}{\text{Standard}} \times \text{Dilution of unknown} \times 5 = \text{mg. bilirubin per liter of serum (with dilution type colorimeter)}$$

### Standard for the quantitative reaction:

#### *Solution 1:*

Ammonium ferric alum . . . . .	0.1508 gm.
Concentrated hydrochloric acid . . . . .	50 cc.
Distilled water . . . . .	q. s. ad. 100 cc.

#### *Solution 2:*

Of solution No. 1 . . . . .	10 cc.
Concentrated hydrochloric acid . . . . .	25 cc.
Distilled water . . . . .	q. s. ad. 250 cc.

(Keeps about one month)

Make standard fresh daily.

Of solution No. 2 . . . . .	3 cc.
10 per cent ammonium sulphocyanate <i>or</i>	
20 per cent potassium sulphocyanate . . . . .	3 cc.
Ether . . . . .	12 cc.

<sup>1</sup> As read from the supernatant alcoholic solution in the graduated centrifuge tube.

Shake thoroughly. The ether extracts the color from the solution and forms a supernatant layer which may be used in colorimetric comparison. The standard matches in color a dilution of 5 mg. of bilirubin per liter. (Plate VII.)

McNee and Keefer<sup>1</sup> have obtained a permanent and more satisfactory standard by the use of cobaltous sulphate. They dissolve 2.161 gm. anhydrous cobaltous sulphate in 100 cc. of water. This standard also represents the color given by 5 mg. bilirubin per liter. Due to difficulties encountered in obtaining cobaltous sulphate with the correct amount of water of crystallization (7 H<sub>2</sub>O), Hall suggests making an aqueous solution somewhat deeper in color than the ether standard, comparing in a colorimeter and diluting to match the color in the ether standard. The addition of 0.5 cc. of sulphuric acid per 100 cc. produces a solution of permanent color.

Greene, Snell and Walters favor the use of a modification of the van den Bergh test as advised by Thannhauser and Anderson<sup>2</sup> and prefer to make bilirubin estimations in terms of milligrams per cent. It is as follows: To 2 cc. of serum is added 1 cc. of the freshly prepared sulphanilic reagent. The resulting color permits the reading of the test in terms of the direct or indirect reaction. Then 2 cc. of a saturated solution of ammonium sulphate is added to help precipitate the serum proteins, followed by 10 cc. of a 96 per cent ethyl alcohol. This produces a prompt intensification of the color corresponding to the indirect reaction of van den Bergh. The contents of the tube are then centrifugalized and the clear supernatant fluid compared colorimetrically with an ethereal solution of ferric sulphocyanid, prepared similarly to the ethereal solution on the preceding page. By this method the loss of bilirubin in the precipitate is largely eliminated. One mg. per cent is equivalent to 2 units (1 unit is equal to 1 in 200,000 content of bilirubin).

In practically no instances will there be no color reaction in the indirect test since the test will detect 1 part bilirubin in 1,500,000 (about 0.7 mg. per liter). As stated previously in normal individuals, the bilirubin content of the blood serum lies between 1 in 500,000 and 1 in 1,000,000 (about 1.5 mg. per liter of serum). A unit of bilirubinemia is a term introduced by van den Bergh, indicating an arbitrary amount of bilirubin in the serum equal to a dilution of 1 in 200,000 (5 mg. of bilirubin per 1000 cc. serum).

<sup>1</sup> McNee, J. W. and Keefer, C. S.: The Clinical Value of the van den Bergh Reaction for Bilirubin in the Blood, *British Med. Jour.*, July 11, 1925, p. 52.

<sup>2</sup> Thannhauser, J. S. and Anderson, E.: Methodik der quantitativen Bilirubinbestimmung in menschlichen Serum, *Deutsch. Arch. f. klin. Med.*, 1921, **137**, 179.

## PLATE VII



Color Reaction in van den Bergh Test.

Tube No. 1 illustrates the deep reddish-violet color obtained in prompt direct van den Bergh reaction after the qualitative method. Patient had obstruction of the common duct by stone. Second tube: shows layer formation during the quantitative determination, after addition of the diazo reagent, alcohol and ammonium sulphate. Comparison in the colorimeter revealed 56 mg. bilirubin per liter of serum. Tube No. 3 illustrates a negative direct reaction in a practically normal individual. The color is a light pink as contrasted to the deep reddish-violet color (prompt direct) obtained in the patient with obstruction of the common duct. The fourth tube shows the layer formation after centrifugalizing. Quantitative estimation revealed 2.5 mg. bilirubin per liter of serum (slightly high but within normal limits).





The indirect test serves both to measure the amount of bilirubin and to develop a color with bilirubin in the presence of alcohol which gives none in the direct reaction. It is a means of identifying cases of hemolytic jaundice and demonstrates latent jaundice. McNee and Keefer<sup>1</sup> issue the precaution that the serum should be fresh, but Hall<sup>2</sup> finds no change in the type of reaction in sera which have been standing as long as two or three months.

The cause of the difference in the two reactions of the van den Bergh is not fully understood. Van den Bergh originally considered that there were two kinds of bilirubin, depending upon the source—whether hemolytic or obstructive. Collinson and Fowweather<sup>3</sup> feel that they have proof of the existence of two forms and express the view that “while the bilirubin giving the prompt direct van den Bergh reaction is an alkali salt, which we believe is probably the ammonium salt, the form which is responsible for the indirect reaction (that is, in presence of alcohol and after precipitation of protein) is the free acid.” Rosenthal states “by ultra filtration experiments I have found that they (meaning the two forms of bilirubin) circulate in the blood firmly bound to the serum proteins. This prevents their elimination by the kidneys. Bile salts by their effects on surface tension are able to liberate bilirubin and these dye stuffs from their absorption compound with the proteins so that they can be further excreted by the liver.” Hall suggests that the presence of bile salts in the blood of patients suffering from obstructive jaundice, and their absence in hemolytic jaundice may be an important factor in the explanation of the two reactions.

Uniformly, in cases of obstructive jaundice, especially if they are complete, a prompt direct reaction is always obtained. Concentration of bilirubin in the serum may be as high as 1 in 4000 (50 units). This concentration is equal to that noted in the bile obtained from biliary fistulæ. McNee and others have noted that bile pigment appears in the urine whenever the content of the serum reaches about 4 units (1 in 50,000) except in hemolytic jaundice. Below this figure, biliuria is absent and a condition of latent jaundice may exist. Hall<sup>4</sup> reports many observations on patients with acute cholangitis all of which yielded immediate direct reactions.

<sup>1</sup> McNee, J. W., and Keefer, C. S.: *Loc. cit.*

<sup>2</sup> Hall, W. W.: *Loc. cit.*

<sup>3</sup> Collinson, G. A. and Fowweather, F. S.: *An Explanation of the Two Forms of Bilirubin Demonstrated by the van den Bergh Reaction*, *British Med. Jour.*, June 26, 1926, p. 1081.

<sup>4</sup> Hall, W. W.: *Loc. cit.*

COMPILATION OF RESULTS OF PHENOLTETRAIODOPHTHALEIN AS COMPARED WITH THE OTHER MOST IMPORTANT TESTS OF HEPATIC FUNCTION AS TAKEN FROM THE LITERATURE.

	Phenoltetraiodophthalein.	Phenoltetra-chlorophthalein.	Bromsulphalein.	Rose bengal.	Icterus index.	Van den Bergh.	Urobilinogen.	Levulose tolerance.	Widal.
Acute cholecystitis with hepatitis . . . . .	+++ to ++++	++ to ++	+++	+	- to ++	-D to P.D.	++	- to ++	++
Chronic cholecystitis without jaundice . . . . .	- to ++++ (15% -)	- to + (80% -)	- to ++ (30% -)	-	- to +	-D to P.D.	+	- to +	-
Chronic cholecystitis with jaundice . . . . .	++ to ++++	++ to ++	++ to ++++	....	++ to ++++	P.D.	++	++	+
Acute cholangitis . . . . .	+++	++	+++	++	++ to ++++	P.D.	++	++	- to ++
Catarrhal jaundice . . . . .	+++	++	+++	++	++ to +++	Indirect	++	++	- to ++
Carcinoma of liver and gall-bladder . . . . .	- to ++++ (majority +)	- to ++	- to ++ (very few -)	- to ++	++ to ++	-D to P.D. (more P.D.)	++	- to ++	+
Carcinoma of pancreas . . . . .	++ to ++	++	+++	- to ++	++	-D to P.D. (more P.D.)	-	++	- to +
Atrophic cirrhosis . . . . .	+++ to ++++	++ to ++	++	++	++	....	++	++	++
Banti's disease . . . . .	++ to ++++	++ to ++	+	....	++	....	+	++	++
Luetic cirrhosis . . . . .	++	++	++	....	++	....	++	+	+
Hemolytic icterus . . . . .	++ to ++	++	++ to ++	....	++	-D or D.D. P.D. or	++	-	+
Arsphenamine jaundice . . . . .	+++	++	+++	++	++	Biphasic -D or D.D.	++	- to +	- to +
Pernicious anemia . . . . .	+	+	+	....	++	....	+	-	- to +
Liver abscess . . . . .	+++	++	++	....	- to +	....	....	-	-
Polycythemia . . . . .	++	- to ++	++	....	+	-D	-	- to ++	+
Pregnancy . . . . .	- to +	- to +	- to +	....	- to ++	-D	- to +	- to ++	+
Eclampsia . . . . .	- to ++	- to +	- to ++	-	+	....	+	+	-
Typhoid . . . . .	....	....	....	....	....	....	....	-	-
Leukemia . . . . .	....	-	....	....	-	-D	....	-	-
Diabetes . . . . .	- to ++	-	....	....	-	Indirect (few D)	++	+	+
Cardiac decompensation; congestion of liver . . . . .	++	- to +	++	-	- to +				
Nephritis . . . . .	....	....	++	-	-				

EXPLANATORY NOTE.—Positive reactions are recorded as +, ++, +++ or ++++, depending upon the consistency of the results. — Indicates negative reaction. In the van den Bergh column D = direct; P.D. = prompt direct and D.D. = delayed direct.

The van den Bergh test will furnish the same valuable information relative to bilirubinemia in latent jaundice as will the icterus index test. The most important disease included in this type of bilirubinemia is pernicious anemia. Variations of findings extend from 3 to 6 units, with an average of about 4 units. The reaction obtained here is delayed direct or occasionally so weak that it is classified as negative.

In uncomplicated hemolytic jaundice the van den Bergh reaction is always of the delayed direct type or so delayed as to be interpreted as negative. The concentration of bilirubin in the serum does not become so great in hemolytic jaundice as in obstructive jaundice, but frequently may be found in amounts up to 15 or 16 units.

Considerable difficulty is encountered in interpretation of the so-called "biphasic" reactions which occur so frequently, as Thompson<sup>1</sup> and others have observed, in patients whose jaundice is of long duration and clinically of the obstructive type. This does not necessarily indicate an inefficiency of the test, since it is quite possible that as time progresses after appearance of the jaundice, substances including bile salts and bile acids may accumulate to such an extent as to produce actual hemolysis of blood. Therefore, to be correct, the test would need to produce a reaction of the biphasic type.

A slight shadow of doubt is cast upon the assumption that a prompt direct reaction always indicates an obstructive bilirubinemia, by some experiments of Mann and associates. They demonstrated that in dogs whose liver had been removed the serum gives first the indirect, then the biphasic, and finally a delayed reaction, which theoretically should not occur in a purely hematogenous jaundice such as this. Furthermore, experiments of Bloom reveal an inconsistency regarding the interpretation of the indirect and direct reactions. He found that in dogs whose kidneys and gall bladder had been removed "the serum in the first day or two after the blocking of the ductus choledochus gives the indirect van den Bergh reaction, and insofar renders doubtful the interpretation of the indirect test when actual tissue icterus is not present. On the other hand, after the scleræ are definitely icteric the direct test is always given." The indirect test became positive usually about two hours after the production of the obstruction.

**3. Fouchet Test.**—This is a qualitative test of bilirubinemia which as devised by Fouchet<sup>2</sup> utilizes the principle of addition of a reagent

<sup>1</sup> Thompson, L. D.: Personal communication.

<sup>2</sup> Fouchet, A.: *Methode Nouvelle de recherche et de dosage des pigments biliares dans le serum sanguin*, *Compt. rend. Soc. de biol.*, 1917, **80**, 826.



to oxidize the bilirubin of the serum. If bilirubin is present in a quantity greater than 1 in 60,000, a green color develops. This is best seen when the serum and reagent are mixed in a white porcelain dish. Fouchet's reagent:

Trichloroacetic acid . . . . .	5 gm.
Water . . . . .	20 cc.
Ferric chloride . . . . .	2 cc.

The test is not very delicate since many times the normal amount of bilirubin must be present before a positive test is obtained. Accordingly, Shattuck, Browne and Preston found it unreliable for testing minor grades of bilirubinemia.

4. **Urobilinogen and Urobilin Test.**—A knowledge of the mechanism of formation of these pigments is necessary to understand the relation of urobilinogenuria to liver disease. The production of urobilinogen and urobilin in the intestinal tract by the action of bacteria upon bile pigments has been described elsewhere in this chapter. This readily explains the absence of urobilinogenuria in patients with obstructive jaundice, because no bile pigment reaches the intestine to act as the source of urobilinogen. It should be emphasized that urobilinogen is found only in very small amounts in normal urine. Urobilin is never found in normal urines and only in very small amounts in freshly voided specimens even in pathological conditions (such as hepatic disease). It is also agreed that uncomplicated and mild cases of duct obstruction do not create much urobilinogenuria or urobilinuria. It occurs, as previously stated, in largest amounts in cases of jaundice of hemolytic origin.

In 1868 Jaffe<sup>1</sup> described the appearance of urobilin in the urine. Many years later, Friedrich Mueller<sup>2</sup> obtained urobilinogen by bringing bilirubin in contact with peptone solution and putrefactive bacteria. Whipple<sup>3</sup> and Hooper,<sup>4</sup> however (in 1922), questioned the intestinal formation of urobilinogen and its absorption into the portal circulation. But Wallace and Diamond,<sup>5</sup> however, feel that the experiments of Ladage<sup>6</sup> consisting of the appearance of a marked increase of urobilinogen in the urine, after feeding 100 mg. of

<sup>1</sup> Jaffe, Max: Urobilin, *Virchow's Arch. f. path. Anat.*, 1868, **47**, 405.

<sup>2</sup> Mueller, Friederich: *Ztschr. f. klin. Med.*, 1887, **12**, 45.

<sup>3</sup> Whipple, G. H.: Pigment Metabolism and Regeneration of Hemoglobin in the Body, *Arch. Int. Med.*, 1922, **29**, 711.

<sup>4</sup> Hooper, C. W. and Whipple, G. H.: *Am. Jour. Physiol.*, 1916, **40**, 349; *Jour. Exper. Med.*, 1916, **23**, 137.

<sup>5</sup> Wallace, G. B. and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, *Arch. Int. Med.*, 1925, **35**, 698.

<sup>6</sup> Ladage, A. A.: *Bydrage tot de kennis de Urobilinurie*, Dissertation, Leyden, 1899.

urobilin by mouth, is positive proof of intestinal absorption of the substance.

McMaster and Elman<sup>1</sup> have conducted a very thorough and extensive experimental study of the physiology and pathology of urobilin. They have shown that "the normal presence of urobilin in the bile and feces of dogs depends on the passage of bile pigment to the intestine, either through normal channels or by abnormal ones, as when it is fed by the mouth. Complete loss of the bile from the body resulted in the total disappearance of urobilin and urobilinogen from the bile, feces and urine. Total obstruction of the bile flow caused disappearance of the urobilin of the bile and stool. Later, as the animals became deeply jaundiced, the pigment appeared again in very small quantity in the feces." This is presumably explained by the excretion of bilirubin into the intestinal lumen by way of the mucosa, but under abnormal conditions. They state further "the evidence here presented, when taken with that of our previous papers, clearly proves that urobilinuria is an expression of the inability of the liver cells to remove from circulation the urobilin brought by the portal stream, with the result that the pigment passes on to the kidney and urine. Urobilinemia occurs with a far less degree of liver injury than does bilirubinemia."

Proof is therefore offered from several sources that urobilin is produced in the intestinal tract and reaches the liver, where it is again converted to bilirubin. If the liver is incapacitated, the conversion to bilirubin will not take place completely and there will be a spill over of urobilinogen into the renal excretion. However, if there is an excessive blood destruction, even a normal liver may be unable to metabolize pigments completely and urobilin may escape into the urine.

*Test for Urobilinogen.*—Add 4 or 5 drops of Ehrlich's aldehyde solution to 5 cc. of urine and leave it in a dark place for fifteen minutes. If positive, a distinct pink or deep red color will appear. To confirm the test, add a few cubic centimeters of chloroform and shake; if urobilinogen is present the chloroform will become red.

Ehrlich's solution:

Para dimethylamidobenzaldehyde . . . . .	2 gm.
Hydrochloric acid (concentrated) . . . . .	15 cc.
Distilled water . . . . .	15 cc.

*Test for Urobilin.*—Add 10 cc. Schlesinger's solution (supersaturated solution of zinc acetate in absolute alcohol) to the same

<sup>1</sup> McMaster, P. D. and Elman, R.: Studies on Urobilin Physiology and Pathology. Papers I to VI; Jour. Exper. Med., 1925, **41**, 503; 1925, **41**, 719; 1925, **42**, 99; 1926, **42**, 619; 1926, **43**, 753.

amount of urine and filter. If urobilin is present a green fluorescence will be seen.

McMaster and Elman have devised a method of quantitative determination of urobilin in the urine, feces or bile. They oxidize the urobilinogen to urobilin by the addition of 1 or 2 drops of tincture of iodine and make the determination by comparing the fluorescence at great dilution with a standard containing acriflavine which has been calibrated against pure urobilin.

Urobilinogen also can be determined quantitatively by the spectroscopic method through the absorption bands produced by the reaction with Ehrlich's solution. Wallace and Diamond likewise have devised a method of quantitative estimation by a dilution test dependent upon Ehrlich's aldehyde reaction. The reading is made by looking through the mouth of the tube, holding the tube obliquely against a white background. The determination is expressed in terms of the greatest dilution of the urine in which the pink color is present. Any specimen of urine giving a color in dilutions any greater than 1 in 20 is considered pathological. This test is dependent on urobilinogen and not urobilin, since urobilin is never found in freshly voided urine. Wallace and Diamond noted further that if a urine specimen containing urobilinogen were allowed to stand away from strong sunlight and in the cold, only a fifth of the urobilinogen disappeared in twenty-four hours. They also found that in parenchymatous changes of the liver such as those induced by chloroform, there occurs a marked increase in the urobilinogen of the urine. Clinically the highest dilution figures were obtained in cases of cholangitis including catarrhal jaundice. Moderate amounts of urobilinogen were found in cases of cirrhosis, hemolytic anemias and chronic hepatitis associated with disease of the appendix and gall bladder. No urobilinogen was found in the patients having mechanical jaundice such as stone in the common duct or carcinoma of the pancreas.

Litzenberg<sup>1</sup> found a positive urobilinogen test in the urine in 30 per cent of normal pregnant women. He interprets this as an indication of slight liver damage in some cases of pregnancy.

5. **Bilirubinuria.**—The presence of bilirubin<sup>1</sup> in the urine is obviously preceded by a hyperbilirubinemia. The exact threshold of the kidneys is undoubtedly variable. Usually the presence of bilirubin in the blood in a concentration of 1 in 50,000 (roughly ten times the normal amount) produces a bilirubinuria. It must be

<sup>1</sup> Litzenberg, J. C.: A Study of Liver Function in Normal Pregnancy, *Am. Jour. Obst.*, 1916, **73**, 228.

emphasized, however, that practically no bilirubin is ever present in the urine of patients with hemolytic jaundice. A few authorities state that bilirubinuria and jaundice appear at about the same time. Most, however, declare that bilirubinuria precedes jaundice (probably dependent upon the delicacy of the particular test used). It is very probable that the threshold of the kidney varies in a manner depending upon the presence or absence of minor pathological changes.

Bile pigments impart to the urine a greenish-yellow or light brown color, which is more noticeable in the foam upon shaking. Casts, sediment, etc., likewise assume a yellowish-brown color in the presence of a bilirubinuria.

There are numerous tests for the presence of bilirubin in the urine. Two of the simpler ones as described by Todd<sup>1</sup> are as follows:

*Smith's Test.*—Overlay the urine with tincture of iodine diluted with nine times its volume of alcohol. An emerald-green ring at the zone of contact shows the presence of bile pigments.

*Gmelin's Test.*—This consists of bringing slightly yellow nitric acid into contact with the urine. A play of colors, of which green and violet are the most distinctive, denotes the presence of bile pigment. Blue and red may be produced by indican and urobilin.

The value of the determination of bilirubin in the urine has been emphasized by Leveruf and Berceanu<sup>2</sup> who applied clinically the test of Grimbert and Delbet. To 10 cc. of urine add 1 cc. of barium chloride. To the precipitate add 1 cc. of 95 per cent alcohol and 1 drop hydrochloric acid. Place in a hot water-bath for one minute. If the mixture turns green, pigment is present. If a colorless or pink color results, no pigment is present. If a brown color is obtained, the presence of bilirubin is questionable, but can be determined by further treatment of the solution.

Leveruf and Berceanu state that with the application of this test, a diagnosis of gall-stone colic can be made within a few hours after the onset of the symptoms, and long before the appearance of jaundice. They advise collection of the urine in hourly samples two to ten hours after the onset of the attack because a very satisfactory test can be obtained by the fourth or fifth hour.

**6. Hemoglobin Test.**—A method was devised by Barlocco<sup>3</sup> consisting of the injection into the blood stream of dissolved isotonic

<sup>1</sup> Todd, J. C.: *Clinical Diagnosis*, W. B. Saunders Company, Philadelphia, 1918, p. 180.

<sup>2</sup> Leveruf, J. and Berceanu, D.: *Un procédé simple pour faire le diagnostic des calculs du choledeque à symptômes frustes*, *Rev. de chir.*, 1925, **63**, 422.

<sup>3</sup> Barlocco: Quoted by Maragliano, E.: *Closing Lecture of Clinical Medicine Course*, *Riforma medica*, 1922, **38**, 721; *abstr. Jour. Am. Med. Assn.*, 1922, **79**, 1369.



hemoglobin. In normal individuals this induces a slight urobilinuria and no change in the bilirubin content of the blood. In patients with liver disease a transient bilirubinemia follows. It may be so intense that macroscopic jaundice is produced. Somewhat the same results are obtained by the introduction of hemolyzed blood into the duodenum or stomach.

**7. Injection of Bilirubin.**—Bergmann<sup>1</sup> has suggested a method of determining hepatic function, consisting of observations on rate of excretion of bilirubin by the liver, after intravenous injection of the pigment. He found that a dose of 0.07 gm. was insufficient to raise the concentration of the pigment in the blood above the renal threshold. It was observed that after acute or chronic alcohol poisoning, there was a marked delay in elimination of the bilirubin. However, the present difficulty and expense entailed in the isolation of bilirubin, offers a very significant handicap in the development of the method.

**Carbohydrate Tests.**—Between the years 1870 and 1900, the numerous articles appearing in the literature regarding the feeding of carbohydrates as a test for liver function intimated that a direct relation had been established between the metabolism of carbohydrates and the function of the liver. However, a great difference of opinion existed as to the value of the test. It remained for Strauss<sup>2</sup> in 1901, who, utilizing Sachs's<sup>3</sup> experiments relative to the intolerance of dehepatectomized frogs to levulose, demonstrated that the cause of the discrepancies was the difference in the kind of sugar used. Strauss recognized that there were mechanisms elsewhere in the body than the liver for the glycogen formation from galactose and glucose, but that the formation of glycogen from levulose was dependent almost entirely upon the liver. He noticed the appearance of a glycosuria after feeding levulose to patients having liver disease. Jacobson at a later date found that dogs upon which an Eck's fistula had been performed (thereby crippling the function of the liver) tolerated levulose poorly.

The experiments of Mann and his associates, as previously stated, further demonstrated the striking influence of the liver upon carbohydrate metabolism by the appearance of a severe hypoglycemia following hepatectomy in dogs. The influence of the pancreas

<sup>1</sup> Bergmann, G. V.: Zur funktionellen Pathology der Leber insbesondere der Alcohol-Atiologie der Cirrhose, *Klin. Wehnschr.*, 1927, **6**, 776.

<sup>2</sup> Strauss, H.: Zur Funktionsprüfung der Leber, *Deutsch. med. Wehnschr.*, 1901, **27**, 757.

<sup>3</sup> Sachs, H.: Ueber Bedeutung der Leber für die Verwerthung der veraschiedenen Zuckerarten im Organismus, *Ztschr. f. klin. Med.*, 1899, **38**, 87.

and muscle upon carbohydrate metabolism detracts considerably from the possibility of specificity of any of the carbohydrate tests.

1. **Levulose Test.**—Strauss originally administered 100 gm. of levulose on an empty stomach, and tested the urine voided during the next four hours for sugar by the Seliwanoff test. Tallerman<sup>1</sup> and others have modified the test by administering, by mouth, 45 gm. in 100 cc. of water after a similar starvation period. Four blood samples are collected at half-hour intervals. Estimations of glycosuria are also made, but have been found to add very little to the data obtained from the blood-sugar curve. King<sup>2</sup> found an average rise of 8 mg. per 100 cc. of blood in normal individuals. In patients with abnormal livers, including portal cirrhosis, carcinoma of the pancreas, catarrhal jaundice, cholangitis, etc., the curve rose as much as 80 or 90 mg. Accordingly, King's conclusion was that "the test is therefore of considerable value as an index of the functional capacity of the liver." On the contrary, Rowntree, Hurwitz and Bloomfield<sup>3</sup> and others find the test of inconsistent value.

2. **Galactose Test.**—This test was first employed in 1906 by Bauer.<sup>4</sup> As used by Davies,<sup>5</sup> the technique is as follows: The sugar should be tested beforehand for its rotary power, which should be at least a specific index of 76 degrees. Forty grams are dissolved in 400 cc. of water and given to a fasting patient, after a fasting sample of blood has been obtained. Procure blood specimens every half hour for two hours after the ingestion of the sugar. Collect urine. Davies found practically no rise in the blood-sugar curve in normal individuals (never more than 30 mg. per 100 cc. of blood). In patients suffering from hepatic cirrhosis, catarrhal jaundice and cholangitis a definite rise varying from 20 to 120 mg. was obtained. Obstructive jaundice in the early stages produces no rise. It is the opinion of Davies and others that the test is only of minor value. Its value as a test of hepatic function is quite certainly less than that of the levulose test.

<sup>1</sup> Tallerman, K. H.: The Levulose Test for Liver Efficiency, *Quart. Jour. Med.*, 1923, **17**, 37.

<sup>2</sup> King, G.: A Study of the Levulose Tolerance Test for Hepatic Efficiency, *Lancet*, 1927, **212**, 385.

<sup>3</sup> Rowntree, L. G., Hurwitz, S. H. and Bloomfield, A. L.: Experimental and Clinical Study of the Value of Phenoltetrachlorophthalein as a Test for Liver Function, *Bull. Johns Hopkins Hosp.*, 1913, **24**, 327.

<sup>4</sup> Bauer, R.: *Wien. med. Wehnschr.*, 1906, **56**, 2537, quoted by Davies.

<sup>5</sup> Davies, D. T.: Some Observations on the Diagnosis of Hepatic Disorders, *Lancet*, 1927, **212**, 380.

3. **Glucose Test.**—Arnoldi<sup>1</sup> has reported his experiences with the ingestion of glucose, relative to the bilirubin content of the blood. After the ingestion of 20 gm. glucose there is produced a hyperbilirubinemia. He feels that pathological conditions of the liver can be determined by the type of rise obtained. Presumably, the ingestion of the sugar throws a sufficient load upon the liver to impair slightly the excretion of bilirubin by the hepatic cells. The specificity of the test would appear to be too low to allow of much accuracy of results.

**Tests Dependent upon Disturbed Nitrogen Metabolism. (Nitrogen Partition Studies.)**—Although it has been proven quite conclusively that the liver is an important organ in the nitrogen metabolism of the body no tests have been devised which yield results consistent with the amount of liver damage. Even more discouraging is the fact that consistent nitrogen figures cannot be obtained in patients suffering from the same diseases and presenting clinical evidence of an equal amount of liver damage. An explanation suggests itself that in the human, other organs have an overlapping function in nitrogen excretion, but to a degree which varies in different individuals and different diseases. A very severe liver damage would therefore be required to produce changes in nitrogen excretion.

Studies have been made with urea, ammonia, amino-acids, non-protein nitrogen, and uric acid content in the blood and urine. Normally, urea nitrogen makes up 40 to 60 per cent of the total non-protein nitrogen of the blood. It was originally thought that if it fell below 40 per cent, especially if a coincident increase in amino-acid and ammonia nitrogen occurred, there was evidence of liver disease. Rubenstone and Tuft<sup>2</sup> made estimation of urea nitrogen as compared to the total non-protein nitrogen in patients with various liver disease. They found that "in patients with advanced liver disease, low urea and comparatively high non-protein nitrogen values were obtained, but, in patients with lesser grades of hepatic disease, the proportion was usually within normal limits." Greene and Conner<sup>3</sup> likewise obtained inconsistent data. They found "no characteristic changes from the normal in the non-protein nitrogenous constituents of the blood in cases of pernicious anemia, hemolytic jaundice or splenic anemia." They state

<sup>1</sup> Arnoldi, W.: Glucose Test of Liver Function, *Münch. med. Wehnschr.*, 1925, **72**, 1414; abstr. *Jour. Am. Med. Assn.*, 1925, **85**, 1172.

<sup>2</sup> Rubenstone, A. I. and Tuft, Louis: A Comparative Study of Liver Functional Tests, *Jour. Lab. and Clin. Med.*, 1926, **11**, 671.

<sup>3</sup> Greene, C. H. and Conner, H. M.: Diseases of the Liver. V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System, *Arch. Int. Med.*, 1926, **38**, 167.

further: "The blood urea and total non-protein nitrogen were increased following a hemolytic crisis in one patient with pernicious anemia. The urinary output of this patient was adequate and the blood urea returned toward normal as the jaundice disappeared. Similar changes were observed in the cases of polycythemia vera during treatment with phenylhydrazine. The changes in both instances were apparently determined by an increased destruction of erythrocytes and a flooding of the organism with the products of protein catabolism."

In animals, Mann and Bollman<sup>1</sup> discovered that there was a definite relation of the uric acid content of the blood and its excretion in the urine to hepatic disease and used it as a test of function. They remark that "following the intravenous injection of 40 mg. of uric acid for each kilogram of body weight of the normal dog, there is a rapid disappearance of the excess uric acid in the blood and only a very small increase in the uric acid in the urine. When this amount of uric acid is injected into a dog having an Eck fistula, the disappearance of the uric acid is somewhat delayed and a slight increase in uric acid excretion occurs. Further reduction of the amount of hepatic tissue gives rise to greater delay in the disappearance of the injected uric acid from the blood, and the urinary excretion of the uric acid is increased."

They can foresee two objections to the application of this test to humans: (1) Large injections of uric acid produce severe lesions in the kidneys and interfere with excretion; (2) lesions of the kidneys may cause retention of uric acid as uricacidemia in man, whereas in the dog, kidney lesions have no influence on the rate of disappearance of uric acid from the blood. As has been mentioned on page 351, Greene has been unable to find any relation of the metabolism of urea and uric acid to hepatic disease in man.

Cohen and Levin<sup>2</sup> have recently recommended observation of the blood-urea curve following the ingestion of 1 gm. protein per kilo. of body weight as a means of determining impairment of hepatic function, as suggested by Mann and associates. After giving 1 gm. protein (chicken) per kilo., they found a normal increase of 50 to 70 per cent in the blood-urea content. In patients suffering from hepatic disease, the rise was much less.

<sup>1</sup> Mann, F. C. and Bollman, J. L.: Liver Function Tests, Arch. Path. and Lab. Med., 1926, **1**, 681.

<sup>2</sup> Cohen, P. and Levin, S. J.: The Protein Test for Urea Formation Function of the Liver, Arch. Int. Med., 1927, **39**, 787.



**Test of Function of Detoxification.**—1. **Widal Test.**—In 1920, Widal and associates<sup>1</sup> introduced the so-called, hemoclastic or proteopexic test of liver function. Their technique consists of taking a leukocyte count, pulse and blood-pressure readings before the ingestion of 200 cc. of milk. The patient should fast ten or twelve hours before the test. The above readings are repeated every half hour for two or three hours. Normally a slight post alimentary leukocytosis takes place. If liver impairment is present, there should occur a drop in the white-cell count and a decrease in the pulse and blood-pressure readings. The leukocyte count has proved to be the only observation of any value. It begins to decrease in about twenty minutes and returns to normal in about one and a half hours.

The explanation of the fall in leukocyte count and blood-pressure is thought to be the inability of the liver, in the presence of disease, to remove the incompletely disintegrated proteins, albumoses, etc., which are brought to it through the portal vein after the milk meal. When these proteins escape into the blood a reaction occurs similar to anaphylaxis. A drop of 50 per cent or more may occur in the leukocyte count.

Rubenstone and Tuft<sup>2</sup> obtained positive results in severe cases of carcinoma of the liver but negative results in catarrhal jaundice. Positive tests were also obtained in cases of arthritis, eczema, etc., which should have had no hepatic damage. Feinblatt<sup>3</sup> and Piersol and Bockus also were unable to obtain reliable results from the test.

2. **Conjugation Tests.**—Delprat and Whipple<sup>4</sup> have investigated the excretion of hippuric acid following administration of sodium benzoate to animals whose livers had been damaged with chloroform. They varied the dose from 0.05 to 0.5 gm. per kilogram of body weight. Both oral and intravenous administrations were tried. They found that in animals having severe liver injury there was a delay in the synthesis and excretion of hippuric acid in the five-hour period following the administration of the sodium benzoate. They concluded that other organs in the body took part in this synthesis and that accurate data concerning injury to the liver could not be obtained.

<sup>1</sup> Widal, F., Abrami, P. and Ianeovesco, N.: *Digestion Hemolysis Test for Insufficiency of Liver*, *Presse méd.*, 1920, **28**, 893.

<sup>2</sup> Rubenstone, A. I., and Tuft, Louis: *A Comparative Study of Liver Functional Tests*, *Jour. Lab. and Clin. Med.*, 1926, **11**, 671.

<sup>3</sup> Feinblatt, H. M.: *Arch. Int. Med.*, 1924, **33**, 210, quoted by Rubenstone and Tuft.

<sup>4</sup> Delprat, G. D. and Whipple, G. H.: *Studies of Liver Function; Benzoate Administration and Hippuric Acid Synthesis*, *Jour. Biol. Chem.*, 1921, **49**, 229.

The conjugation of various other chemicals, including especially phenolic substances such as salicylic acid, camphor and cresol have been investigated in the presence of liver damage. Roger and Chiray<sup>1</sup> administered camphor and measured the excretion of camphor glycuronic acid. Conjugation was delayed or diminished in patients with hepatic disorders. Foster and Kahn<sup>2</sup> fed thymol and interpreted the increase of ethereal sulphates in the urine as an index of the conjugation of the thymol by the liver.

**Miscellaneous Tests.**—1. **Bile Salts in the Urine and Blood.**—The possibilities of the importance of such tests in the differentiation between hemolytic and obstructive jaundice, as well as the detection of early or latent jaundice can easily be conceived. Theoretically, bile salts should be present in the blood and urine early in cases of obstructive jaundice but the proof and utilization of this assumption cannot be fully realized on account of the lack of a delicate test for the salts. The Hay test for bile salts in the urine, as used by Berger, Cohen and Selman<sup>3</sup> is as follows: Dry, finely powdered, sublimed sulphur is sprinkled into a freshly voided morning specimen of urine, which has been collected in a clean dry beaker. The rapidity with which the sulphur particles fall to the bottom is taken as an index of the amount of bile salts in the urine. If the test is positive, the granules will begin to fall to the bottom immediately. In cases of obstructive jaundice due to stone in the common duct, and carcinoma of the pancreas, Berger, Cohen and Selman obtained a positive result in 80 per cent of the cases. In a series of miscellaneous types of jaundice a smaller percentage of positive tests was obtained. We interpret the inconsistency of positive results as being due more to a lack of delicacy of the test rather than to an absence of the salts in the cases of obstructive jaundice.

Foster and Hooper<sup>4</sup> have devised a method for the quantitative determination of bile acid excreted in the bile, but this method is not adaptable to the smaller amount of bile acids in the urine and blood.

2. **Fragility Test.**—This can scarcely be included as a test of liver function, but is of such importance in the differential diagnosis of

<sup>1</sup> Roger, H. and Chiray, M.: *La glycuronurie normale et pathologique; ses variations dans la cirrhose et le diabete*, Bull. Acad. de méd., 1915, **73**, 446.

<sup>2</sup> Foster, C. S. and Kahn, M.: *A Study of the Tests of Liver Function*, Jour. Lab. and Clin. Med., 1916, **2**, 25.

<sup>3</sup> Berger, S. S., Cohen, M. B. and Selman, J. J.: *Liver Function Tests*, Jour. Am. Med. Assn., 1926, **86**, 1114.

<sup>4</sup> Foster, M. G. and Hooper, C. W.: *The Metabolism of Bile Acids. I. A Quantitative Method for Analysis of Bile Acids in Dogs' Bile*, Jour. Biol. Chem., 1919, **38**, 355.

the two types of jaundice that it is mentioned here. Ribierre in 1903 first described a simple but accurate method for the measurement of the resistance and fragility of erythrocytes.

The method described by Todd<sup>1</sup> is simple, brief and accurate: Allow 1 or 2 cc. of blood to flow from a vein, directly into a graduated centrifuge tube containing about 2 cc. of citrated salt solution (sodium chloride, 0.9 gm.; sodium citrate, 0.5 gm.; water, 100 cc.) and mix gently. Wash the corpuscles twice with 0.7 per cent salt solution by centrifugalizing and pipetting off the supernatant fluid, the last time leaving a volume of fluid equal to the volume of corpuscles. Mix gently. Arrange a series of 11 small test-tubes and place in each, 1 cc. of sodium chloride solution varying in strength from 0.2 per cent in the first tube to 0.7 per cent in the last. To each tube add 0.1 cc. of the suspension of washed corpuscles and mix by inverting once or twice. Instead of using washed corpuscles, some workers simply add 1 drop of blood from a skin puncture to each tube. Let stand two hours at room temperature. At the end of that time the corpuscles will have settled to the bottom and hemolysis may be recognized by the color of the supernatant fluid; faintly pink, if hemolysis is partial; red, with little or no sediment, if it is complete.

With normal blood, hemolysis usually begins in the tube containing 0.45 per cent salt solution and is complete in that containing 0.35 per cent. The most striking change in the time of hemolysis is seen in hemolytic jaundice (*e. g.*, familial jaundice) when the resistance of the erythrocytes decreases so much that hemolysis begins in the tube containing 0.6 or 0.65 per cent salt solution, and is complete at about 0.4 or 0.45 per cent. The cells of patients having obstructive jaundice or anemia (primary or secondary) are usually very slightly more resistant than normal. A control series should be conducted, obtaining blood from a normal individual. By so doing, errors in mixing the saline etc., will be detected.

Giffin and Sanford<sup>2</sup> have devised a method, as modified from Ribierre's original procedure, using 0.5 per cent salt solution and distilled water to make solutions varying between 0.5 per cent and 0.25 per cent in concentration. One drop of blood is added to each tube. A control series from a normal person should be arranged beside the patients' tubes. They found that 22 of 25 cases of

<sup>1</sup> Todd, J. C.: Clinical Diagnosis, W. B. Saunders Company, Philadelphia, 1918, 324.

<sup>2</sup> Giffin, H. Z. and Sanford, A. H.: Clinical Observations Concerning the Fragility of Erythrocytes, Jour. Lab. and Clin. Med., 1919, 4, 465.

hemolytic jaundice revealed a strikingly decreased resistance. In pernicious anemia the resistance was slightly increased. In 11 cases of obstructive jaundice a slight increase in resistance was discovered.

**3. Determination of Fibrinogen Content of the Blood.**—The liver has a definite influence on the maintenance of fibrinogen, but the exact mechanism is poorly understood. The test as utilized by Rowntree, Hurwitz and Bloomfield is as follows: 25 or 50 cc. of clear plasma obtained by centrifugalizing blood which has been collected in oxalate solution, is heated in a water-bath at 59° C. for twenty to thirty minutes. Fibrinogen is thrown out as a white flocculent precipitate, is collected on a Gooch crucible, washed with H<sub>2</sub>O, alcohol and ether, dried and weighed. Owing to the probability of sources of fibrinogen other than the liver, not much value can be placed in the method as a test of hepatic function.

Lee and White<sup>1</sup> have popularized a simple but efficient method of determining the coagulation time: 1 cc. of blood is withdrawn from an arm vein, with a syringe which has been previously washed in physiological salt solution, and emptied into a small glass test-tube (8 mm. in diameter) which likewise has been carefully washed in physiological salt solution. The tube is rotated endwise every thirty seconds and that point at which the blood no longer flows when inverted is taken as the end-point. They obtained a clotting time of six and a half minutes in normal individuals. The clotting time of patients with jaundice and hepatic diseases varied considerably; those with only slight jaundice usually were within normal limits and those with marked jaundice were often delayed as long as nine to ten minutes beyond normal. Presumably, the chief factors in the delayed clotting time in jaundice with hepatic injury are the increased bile salt content of the blood and the decreased amount of fibrinogen. It is thought by some observers, however, that in the presence of jaundice, the bile pigment which is retained in excess, couples with the calcium and therefore decreases the available calcium, which is a link in the clotting system.

**4. Ferment Tests.**—It is agreed that the liver lends aid in the maintenance of numerous enzymes, including lipase, and the sugar converting ferments, diastase and amylase, but their origin in other organs renders any quantitative estimation of doubtful value in determining hepatic function. Whipple, Mason and Peightal<sup>2</sup> have

<sup>1</sup> Lee, R. G. and White, P. D.: A Clinical Study of the Coagulation Time, *Am. Jour. Med. Sci.*, 1913, **145**, 495.

<sup>2</sup> Whipple, G. H., Mason, V. R. and Peightal, T. C.: Tests for Hepatic Function and Disease under Experimental Conditions, *Bull., Johns Hopkins Hosp.* 1913, **24**, 207.



demonstrated a marked increase in the amount of lipase in the blood in certain diseases of the liver.

5. **Hemoconia Test of Brulé.**—A discussion of the necessity of bile acids for the absorption of fat is given by Brulé<sup>1</sup> who has devised a method for the estimation of ultramicroscopic blood fat particles (hemoconia) after a fat meal. Snell, Greene and Rowntree,<sup>2</sup> using this method in animal experimentation, report favorably on the test, by obtaining no increase of hemoconia in cases of biliary obstruction, but a normal increase after the reestablishment of the connection between the bile passages and intestine.

6. **Excretion of Tetraiodophenolphthalein.**—Behrend and Heesch<sup>3</sup> have examined the blood, urine and feces of patients for iodine content, after injection of sodium tetraiodophenolphthalein. In healthy subjects iodine was eliminated from the blood in a few hours, and from the urine in ten to twenty hours. The feces contained iodine for about ten days. The excretion of iodine from the blood and in the urine was delayed in patients having hepatic disease.

#### COMMENT AND COMPARISON OF VARIOUS TESTS.

As yet, no methods of determining hepatic function have been found which yield entirely satisfactory results. Because of the diversity of functions of the liver, it is doubtful if a single test will be found, which will furnish an estimation of the functional capacity of an organ as accurately as does the excretion test (dye) for the kidney, since excretion of waste products is the major function of that organ. However, we have encountered certain valuable facts (see pp. 359 and 392) in our use of the excretion of phenoltetraiodophthalein, which offer encouragement. Comparing our results with other dyes, we have concluded that much more information is to be obtained from any dye, by injecting a much larger dose than that ordinarily given, and still stay within the limits of safety. From their vast amount of experimental work with methods for determination of liver function, Mann and Bollman have commented that a larger dose of dye (phenoltetrachlorphthalein and bromsulphalein) offered more opportunity for obtaining results which corresponded to the amount of liver damage, than does the dose advocated for the

<sup>1</sup> Brulé, M.: *Recherches sur les icteres: les retentions biliaries par insuffisance hepatique*, Paris, Masson et Cie, 1922, XIII, quoted by Snell, Greene and Rowntree.

<sup>2</sup> Snell, A. M., Greene, C. G. and Rowntree, L. G.: *Diseases of the Liver. II. Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice*, *Arch. Int. Med.*, 1925, **36**, 273.

<sup>3</sup> Behrend, C. M. and Heesch, O.: *Liver Function Test*, *Med. Klin.*, 1926, **22**, 767; *abstr. Jour. Am. Med. Assn.*, 1926, **87**, 210.

human. They expressed doubt that accurate comparisons could be made between man and animals. Reference has already been made (see page 351) to the findings of Greene and associates revealing conflicting data concerning the metabolism of urea and uric acid in the dog as compared to that of the human being.

Up to the present time, phenoltetraiodophthalein is the only dye which can be used to advantage in the simultaneous production of cholecystograms and determination of hepatic function. The most satisfactory dose for use in this combined method is 40 mg. per kilogram of body weight.

We have observed that patients showing a high retention of phenoltetraiodophthalein in the blood stream after injection of the dye were poor surgical risks. This is more thoroughly discussed elsewhere (see page 392) Laird, Brugh and Wilkerson<sup>1</sup> using phenoltetrachlorophthalein have, independently come to the same conclusion and use the test as an aid in determining the optimum time for operation. They even go further and advise drainage of the common duct through the cystic duct if an extremely high retention is found. They also substantiate the assumption that most patients having poor results from cholecystectomy do poorly because of serious damage to the liver from inflammatory causes. A retention of dye for a considerable period after operation was encountered in patients having unsatisfactory convalescence. They observed a close parallelism between dye retention and clinical symptoms and signs.

The second point of value obtained from the use of phenoltetraiodophthalein in determination of hepatic function has been the almost constant manifestation of dye retention in cases of cholecystitis. From the standpoint of positive findings there has been a close parallelism between the dye test and cholecystograms. The amount of retention usually varies in a direct ratio with the severity of symptoms. (See pages 392 to 398 for detailed results.) Unfortunately, the introduction of phenoltetraiodophthalein has been too recent to allow us to include the experience of others.

Of all the tests enumerated, we feel quite certain that the dye tests (including chiefly phenoltetraiodophthalein, bromsulphalein, and phenoltetrachlorophthalein) and methods of estimating bilirubin (van den Bergh and icterus index tests) are of the most value, and will show a more consistent correlation with clinical and pathological findings than other tests. The applicability of the bilirubin tests is

<sup>1</sup> Laird, W. R., Brugh, B. F. and Wilkerson, W. V.: Liver Function Studies and their Clinical Correlation, *Ann. Surg.*, 1926, **84**, 703.

confined almost entirely to patients with jaundice (gross or latent). The dye tests show positive reactions in a much larger number of diseases of the liver than will the bilirubin tests. As stated previously, we have obtained more satisfactory results with phenoltetraiodophthalein in the dose of 40 mg. per kilo than with bromsulphalein or phenoltetrachlorophthalein, when using the dose advocated by the originators of the tests.

## COMPARISON OF RESULTS OF DYE TESTS.

(Two Tests on Each Patient.)

Cases.	Retention of dye (per cent).*					
	Phenoltetraiodophthalein.		Phenoltetrachlorophthalein.		Bromsulphalein.	
	30 min.	60 min.	15 min.	60 min.	5 min.	30 min.
1. Cholecystitis with jaundice . . .	32	..	..	..	12	3
2. Cholecystitis without jaundice . . .	40	..	..	..	45	5
3. Cirrhosis . . . . .	45	..	..	..	50	10
4. Pregnancy . . . . .	30	..	15	12		
5. Cholecystitis without jaundice . . .	60	..	8	6		
6. Cholecystitis with jaundice . . .	50	..	50	40		
7. Cholecystitis with jaundice . . .	80	..	25	8		
8. Normal . . . . .	12	4	6	0	35	0

All of the cases of cholecystitis were operated on, and the diagnoses confirmed.

The deductions of Greene and associates relative to the comparative values of the various tests in clinical use, are probably of more value than those of any other individual source because of the vast number of tests used, and the detailed extent of application. Greene, McVicar, Rowntree and Walters<sup>1</sup> conducted a series of function tests, including fructose tolerance, nitrogen partition studies, van den Bergh and phenoltetrachlorophthalein, in patients with obstruction of the common duct. Only with the latter two methods did they obtain consistent results of any value. They state "in cases of obstructive jaundice there is a marked retention of phenoltetrachlorophthalein in the blood stream that roughly corresponds to the degree of bile retention. This apparently indicates primarily the effect of bile retention on the liver. After the complete disappearance of the jaundice and return of the serum bilirubin level to

<sup>1</sup> Greene, C. H., McVicar, C. S., Rowntree, L. G. and Walters, W.: Diseases of the Liver. III. A Comparative Study of Certain Tests for Hepatic Function in Patients with Obstructive Jaundice, Arch. Int. Med., 1925, **36**, 418.

normal, there frequently is a persistent slight degree of dye retention that apparently indicates the degree of residual hepatic disturbance remaining in consequence of the jaundice. These two tests give promise of definite clinical usefulness in the study, and particularly the quantitative study, of the functional changes in patients with obstructive jaundice." In a series of patients having carcinoma of the biliary tract or liver, Greene<sup>1</sup> and associates found again that only the dye and bilirubin tests were of value. "It is in the study of patients with carcinoma involving the liver without jaundice that functional tests are of the greatest value, particularly the phenoltetrachlorophthalein test. In the absence of clinical evidence of hepatic involvement, the phenoltetrachlorophthalein test may furnish the only evidence of the existence of metastatic nodules in the liver." We emphasize a statement made by them that positive tests cannot be expected in cases of minor involvement of the liver with carcinoma. Finding normal figures in such cases is to be expected because destruction and necrosis of hepatic cells in any great number does not take place in the presence of mild invasion of carcinoma.

Greene and Conner conducted a series of tests, including fructose tolerance, nitrogen partition studies, serum bilirubin and phenoltetrachlorophthalein, in various diseases of the hematopoietic system. No very reliable results were obtained with any method. In view of the questionable involvement of the liver from the clinical and pathological standpoint, such results would be expected. However the serum bilirubin was found elevated (indirect diazo reaction) in patients with jaundice of hemolytic origin as has been mentioned previously. In leukemia and polycythemia they found slight disturbances in the nitrogen partition studies. In many cases of splenic anemia, the phenoltetrachlorophthalein test revealed retention, indicative of cirrhotic changes in the liver.

In a summary of past experiences, Greene remarks that "disturbance in one type of physiological activity does not necessarily indicate commensurate disturbance in other functions of the liver. The presence of a normal amount of bilirubin in the serum and absence of dye retention will not exclude hepatic disease. Positive tests, on the other hand, are of great value in indicating the probable presence of definite and widespread hepatic damage." He therefore expresses our belief that no single test will be able to detect impairment in each of the various functions of the liver and

<sup>1</sup> Greene, C. H., McVicar, C. S., Walters, W. and Rowntree, L. G.: Diseases of the Liver. IV. Functional Tests in Cases of Carcinoma of the Liver and Biliary Tract, *Arch. Int. Med.*, 1925, **36**, 542.



that the greatest defect lies in the sensitivity of the tests of hepatic function.

Realizing the selectivity of each of the various tests for one particular function of the liver, Rubenstone and Tuft<sup>1</sup> have devised a method for carrying out the icterus index, blood chemistry, levulose tolerance, bilirubin and dye tests at one time with a minimum amount of discomfort to the patient. In agreement with most other reports they also obtained more satisfactory results with the bilirubin and dye tests than with any of the other methods tried.

Berger, Cohen and Selman<sup>2</sup> report experiences with the van den Bergh, Widal, Rosenthal, and urobilinogen tests, as well as determinations of bile salts in the urine. They, too, lament the fact that the various functions of the liver are not equally affected in disease, thereby accounting for inconsistent results. However they found that all the tests were positive, when the hepatic disease was of any consequence.

Authorities differ in expressing the comparative values of the icterus index and van den Bergh test. Barrow, Armstrong and Olds<sup>3</sup> favor the icterus index test. Hall, Greene and others feel that the van den Bergh test is of more clinical assistance than the icterus index test, especially in differential diagnosis. One great advantage of the icterus index test lies in its striking simplicity. Each is primarily a test of bilirubinemia.

#### INFORMATION GAINED FROM THE USE OF PHENOLTETRAIODOPHTHALEIN AS A TEST OF HEPATIC FUNCTION COMBINED WITH CHOLECYSTOGRAPHY.

The series of determinations of hepatic function with phenoltetraiodophthalein upon patients with pathological conditions of the liver has been too small to allow of infallible conclusions, but several features of importance have been consistent.

Probably the most important finding has been the ability to predict to a large extent, the status of operability (*i. e.*, operative risk and optimum time for operation) by the amount of retention of dye in the blood stream following injection. Three of our patients in a series of cases of cholecystitis, who had simultaneous determina-

<sup>1</sup> Rubenstone, A. I., and Tuft, Louis: A Comparative Study of Liver Functional Tests, *Jour. Lab. and Clin. Med.*, 1926, **11**, 671.

<sup>2</sup> Berger, S. S., Cohen, M. B., and Selman, J. J.: Liver Function Tests, *Jour. Am. Med. Assn.*, 1926, **86**, 1114.

<sup>3</sup> Barrow, J. V., Armstrong, E. L. and Olds, W. H.: Further Clinical and Operative Studies of the Icterus Index, *Am. Jour. Med. Sci.*, 1925, **170**, 519.

tions of hepatic function and cholecystographic examination by means of phenoltetraiodophthalein died following cholecystectomy. One of these had been jaundiced for three or four weeks and showed a retention of 90 per cent at the end of thirty minutes. At operation a choledochostomy for stone, and cholecystectomy were performed. The bile in her common duct was colorless—also indicating a severe liver damage. The second patient, who was not jaundiced, revealed a retention of 60 per cent in thirty minutes, and at operation had in addition to cholecystectomy, removal of an intraligamentous cyst of the broad ligament. The third patient, also not jaundiced, revealed a retention of 90 per cent in thirty minutes. At operation duodenal ulcer was found, in addition to cholecystitis; gastro-enterostomy and cholecystectomy were performed. These figures represent the highest retention found in all the patients in this series, upon whom operation was performed. We feel safe in concluding therefore that a high retention of the dye indicates a status of poor operative risk. Operation in such cases should be undertaken only after careful consideration and after the institution of such preoperative measures as will improve the condition of the liver. Of these, glucose in large quantities is the most important. Blood transfusion also is helpful in some cases. Moreover, it would be wise to confine any operative procedure to the minimum which is most imperatively demanded.

We have had occasion to obtain determinations on only one case of so-called catarrhal jaundice. This patient revealed a retention of 90 per cent in one-half hour and represents the highest retention of any group of cases. Pathological findings of severe microscopic changes in catarrhal jaundice support the indication of extreme hepatic damage. See Chapter VI for a discussion of this question. The average retentions of diseases by groups are as follows: (1) Cholecystitis with jaundice 55 per cent in thirty minutes; (2) duodenal ulcer, most of which in this series were associated with cholecystitis, 58 per cent in thirty minutes; (3) carcinoma of liver, 20 per cent in thirty minutes, 15 per cent in sixty minutes; (4) appendicitis with associated hepatitis, 28 per cent in thirty minutes; (5) chronic cholecystitis, without jaundice, 27 per cent in thirty minutes.

A finding which occurred quite constantly was a retention of dye above normal, in 85 patients with gall-bladder disease. In fact, practically 85 per cent of patients, whose cholecystograms indicated a pathological gall bladder, revealed also a retention of dye (phenoltetraiodophthalein) above normal. Almost routinely, the patients

# RESULTS OF DETERMINATIONS OF HEPATIC FUNCTION WITH PHENOLTETRAIODOPHTHALEIN.

Diagnosis.	Cholecystograms.	Hepatic function. Retention of dye.		Remarks.
		30 min.	60 min.	
Cholecystitis without jaundice . . . . .	Pathological	55		Only mild pathological findings in gall bladder; liver grossly normal.
	"	30		
	"	17		
	?Pathological	13		
	Pathological	17	4	Had cholecystectomy and excision of intraligamentous cyst of ovary; died seventh day with atypical symptoms of shock and ileus.
	"	18		
	"	15	8	
	"	30		
	"	20	15	
	"	40		
	"	30		
	"	35	15	
	"	60		
	"	20		
	"	20		
	"	30		
	"	20		
Cholecystitis with jaundice . . . . .	"	17		Had tuberculous peritonitis accompanying severe infection of the gall bladder and scarring of the liver; four and sixteen weeks after operation had 40 and 30 per cent retention respectively; very stormy convalescence.
	"	30		
	"	90	75	
	"	80		
	"	32		
	"	45		
	"	45		Long history of jaundice; died twelve hours after operation in severe shock; postmortem revealed insufficient hemorrhage to account for death.
	"	90		
	"	90		
	Average . .	55		
	Pathological	27	15	
	"	40		
	"	50		
	"	50	30	
	"	90	75	

RESULTS OF DETERMINATIONS OF HEPATIC FUNCTION WITH PHENOLTETRAIODO-PHTHALEIN—*Continued.*

Diagnosis.	Chole- cystograms.	Liver function. Retention of dye.		Remarks.
		30 min.	60 min.	
Atrophic cirrhosis . . .	Pathological	26 35	18 ...	Jaundice. No jaundice—no opera- tion.
	Normal	70	...	No jaundice.
	Pathological	45	...	No jaundice.
	"	60	...	No jaundice.
	Average . .	47		
Luetic cirrhosis . . .	Pathological	50	...	Ascites present.
Catarrhal jaundice . . .	Pathological	90	70	
Carcinoma of pancreas .	Pathological	25	20	Jaundice present.
Carcinoma of liver and omentum . . . . .	"	40	20	No jaundice.
Carcinoma of stomach; slight metastasis to liver	"	28	16	No jaundice.
Carcinoma of gall bladder	"	35	10	Jaundice present for sev- eral weeks.
Carcinoma of pancreas .	"	18	10	Mild jaundice—45 per cent retention in a half hour three weeks later.
Carcinoma of cystic duct and liver . . . . .	"	35		
Carcinoma of liver . . .	"	18	...	No jaundice.
Hypernephroma with ab- dominal metastasis . .	?Pathological	35	15	No jaundice—no opera- tion.
	Average . .	29	15	
Ulcer of duodenum . . .	Normal	23	17	
Duodenal ulcer and chole- cystitis . . . . .	Pathological	60		
Duodenal ulcer and peri- cholecystitis . . . . .	?Normal	90	...	Died third day postoper- ative.
Duodenal ulcer and chole- cystitis . . . . .	Pathological	60		
	Average . .	58		
Abscess of liver . . .	?Pathological	31	16	
Banti's disease . . . .	?Pathological	40	27	Had omentopexy for as- cites; 35 per cent reten- tion one year later.
Diabetes . . . . .	?Pathological	22	...	No operation.
	Pathological	30	...	No operation.
Appendicitis, salpingitis .	Normal	18		
Subacute appendicitis with tender liver . . .	Normal	20		
Subacute appendicitis with tender liver . . .	Normal	35		
Chronic appendicitis with salpingitis and upper abdominal tenderness .	Normal	45		
	Average . .	28		



RESULTS OF DETERMINATION OF HEPATIC FUNCTION WITH PHENOLTETRAIODOPHTHALEIN—*Continued.*

Diagnosis.	Cholecystograms.	Liver function. Retention of dye.		Remarks.
		30 min.	60 min.	
Hemachromatosis; amyloid liver? . . . . .	Indeterminable	20	12	No operation.
Arteriosclerosis (sixty-six years of age) . . . . .	Normal	25		No operation.
50 normal individuals . . . . .	.....	12	4	

The diagnosis was confirmed in all of the patients listed in the above table, unless specified to the contrary in the remarks column.

who presented a long history of illness due to cholecystitis, had a higher retention than those with mild symptoms. An explanation of this can possibly be seen in the fact that hepatitis is practically a constant accompaniment of cholecystitis, as has been shown by one of us. (See Chapter III.) Because of the simultaneous appearance of a pathological gall bladder and impairment of hepatic function, it does not necessarily follow that impairment of the function of the liver tends to produce a pathological series of cholecystograms because of the accessibility of less dye for the gall bladder. On numerous occasions, normal cholecystograms have been found in the presence of a retention of dye as high as 50 or 60 per cent in the blood stream thirty minutes after injection. It is reasonable, however, to suppose that if the damage to the liver became great enough, the amount of dye passing through the common duct would be insufficient to allow of a concentration in the gall bladder which would produce a shadow on the roentgen-ray film. Fried and Whitaker,<sup>1</sup> have demonstrated experimentally that a huge amount of hepatic damage is necessary before the density of the cholecystograms becomes affected.

As can be seen in the table on page 395, patients suffering from duodenal ulcer with accompanying cholecystitis, revealed a very high retention; an average of 70 per cent in thirty minutes. This is to be expected because of the added hepatitis produced by the inflammation accompanying the duodenal ulcer. Considerable scarring was seen over the surface of the liver in all of these cases.

<sup>1</sup> Fried, B. M. and Whitaker, L. R.: The Effect of Liver Damage on Cholecystography in Dogs by the Use of Sodium Tetraiodophenolphthalein, *Arch. Int. Med.*, 1926, **37**, 388.

The most valuable information from the standpoint of differential diagnosis is encountered in jaundice caused by obstruction of the common duct by stone, and carcinoma of the liver. Uniformly the retention is greater in patients having common-duct stone even though the jaundice has been present in the carcinomatous patient for several weeks. Observation after a lapse of time reveals an increase in the retention in the patients having duct obstruction by stone, but almost a stationary reading in patients with hepatic carcinoma, until the terminal stage is reached. The explanation of this phenomenon may easily be the fact that carcinoma implants itself in the liver tissue, but causes no destruction of hepatic cells until the terminal stage is reached when necrosis is produced by pressure, whereas the products of retention when the common duct is obstructed by a stone, produce an immediate and progressive hepatic injury. The presence of infection of the liver in cases of obstruction with stone is very likely the chief factor in the production of greater hepatic damage and dye retention. It is also possible that in the presence of a gradual production of jaundice such as produced by carcinoma, the liver is able to compensate, either by hyperplasia or assistance from other organs. The accuracy of the higher retention, in patients with jaundice, produced by obstruction of the common duct by stone, than in patients with carcinoma of the liver, is supported by the occurrence of more cellular necrosis and infiltration, as seen microscopically in the liver, when the obstruction was caused by stone in the common duct.

In correlation with the above findings, it was noticed that a lower grade of retention was encountered in patients with obstruction of the common duct due to carcinoma of the pancreas than in patients with obstruction caused by stone. It would seem that the same factors as given in the preceding paragraph, should apply here in explaining the difference in retention. Again the presence or absence of infection within the liver would appear to be the controlling factor in the amount of retention.

The well known assumption that jaundice produces damage of the liver is supported by observations revealing a retention of dye above normal in almost every case. It is evident, however, that the intensity or duration of jaundice does not control the amount of retention. In our series, the type of jaundice has been the factor which determined the amount of retention. As stated previously, a higher retention was found in the cases of jaundice produced by stone in the common duct, than in those with obstruction due to

other causes. Since this agrees with microscopic findings, we conclude, that of the two most popular tests (dye and bilirubin) the dye test is probably superior, especially because the chief information gained from the pigment test is the amount of bilirubinemia. There are no indications that the degree of hyperbilirubinemia determines the amount of retention of dye in the blood stream, but accurate quantitative estimations of bilirubin should accompany the dye tests. However, since the two methods are tests of different hepatic functions, one cannot be discarded in favor of the other, but indications furnished by the particular case should determine the choice and value.

## CHAPTER IX.

### SURGICAL TREATMENT OF CHOLECYSTITIS.

**Introduction.**—Originally the surgical treatment of disease of the gall bladder was directed only against the drainage of abscesses originating in a suppurative inflammation of the organ and pointing externally. An account of some of these early procedures is given in Chapter IV. These operations were scarcely different in kind from the incision of any other abscess. On June 15, 1867, somewhat accidentally, John S. Bobbs<sup>1</sup> of Indianapolis started a new era, the era of deliberate surgical attack on the gall bladder. Bobbs opened the abdomen of a woman, aged thirty years, under the mistaken idea that he was going to operate perhaps on an ovarian tumor. The tumor, however, was found to be a large hydrops of the gall bladder which he incised and from which he removed clear fluid and about 50 gall stones. He then closed his incision, and the patient made an uneventful recovery from the operation. According to Tinker,<sup>2</sup> however, the patient though much improved, was still suffering many years afterward from digestive disturbances. Eleven years later (1878) Marion Sims and again in 1879 W. W. Keen both deliberately operated on the gall bladder, but both operations had fatal results. By 1885 Lawson Tait had operated upon no less than 15 patients; and many others had reported 1 or more cases, including Blodgett, Kocher, König, Langenbuch, Courvoisier, another 1 by Keen, Ransohoff, Eddowes, Savage, Gross, Gardner, Wood, etc. From that time on the number of operations rapidly increased. The early operations consisted chiefly of opening the gall bladder, removing stones and other contents and then making a tight closure. The operation was sometimes performed in one stage and sometimes in two stages, the first stage consisting merely of creating adhesions between the gall bladder and the abdominal wall. The operation of "ideal cholecystotomy" (named "cholecystendysis" by Courvoisier) was practised extensively. In this procedure the gall bladder was

<sup>1</sup> Bobbs, J. S.: Trans. Indiana State Med. Soc., 1868, quoted from Courvoisier.

<sup>2</sup> An interesting account of this operation is given by Martin Tinker in the Bulletin of the Johns Hopkins Hospital, 1901, 12, 249.



closed tightly and allowed to drop back into the abdomen. Another procedure which came into some favor early (1887-1890) was the operation of cholecysto-enterostomy, anastomosing the gall bladder to the duodenum to permit artificial but internal drainage of the organ. In 1882, however, Langenbuch<sup>1</sup> for the first time deliberately removed a gall bladder which contained stones and was badly infected; and the patient recovered. Within a year he had performed the operation on 3 more cases. Of the 4 cases, 2 recovered and 2 died, 1 from peritonitis and 1 from an abscess of the choroid plexus. By 1890 as many as 47 cases of cholecystectomy had been reported, according to Courvoisier. Until comparatively recent times the surgical treatment has been directed mainly against gall stones, and in general only those patients were submitted to operation who showed evidence of the most serious effects of cholecystic disease. Nowadays, however, there is evident a tendency to prevent the serious late effects by earlier intervention. This tendency has shown itself in the fact that at the present time less attention is devoted to the question of stones and more attention is given to the importance of infection.

**Preparation of Patients for Operation.**—Patients with diseases of the biliary tract upon whom operations are contemplated often need special attention directed toward their preoperative preparation. These preparations should be concerned particularly with several considerations, the postponement of the operation during an acute stage of inflammation, the improvement of the damaged condition of the liver, the prevention of hemorrhage, and the improvement of any existing diabetic condition.

It is seldom advisable to operate upon a patient with acute cholecystitis. The danger of serious infection and the development of peritonitis is enormously greater following an operation performed on an acutely inflamed gall bladder than if the operation is postponed until the inflammation is quiescent. It is particularly dangerous to perform cholecystectomy in a case of acute cholecystitis. Perforation of the gall bladder occurs so rarely that one is justified in practically every case in waiting for the acute symptoms to subside.

Many of the deaths which occur after operations take place in patients whose livers have been functionally severely damaged. It is well known that one of the important functions of the liver is the protection of the body against poisonous substances which are

<sup>1</sup> Langenbuch, C.: Ein Fall von Exstirpation der Gallenblase wegen chronischer Cholelithiasis, Berlin. klin. Wchnschr., 1882, 19, 725.

formed in the intestine. It has furthermore been established that much of the power of the liver to carry out this detoxicating function depends upon its content of glycogen. (See in this respect the reference on page 213 to work by one of us.) It is therefore highly important to insure a rich supply of glycogen to the liver before undertaking any operation on the biliary tract. The copious administration of carbohydrate is therefore a very important adjunct to the treatment, and it may be most conveniently administered in the form of glucose which, if the occasion demands, may be given intravenously. Since many subjects of cholecystic disease are obese, and since acidosis is particularly prone to develop in such patients after starvation, the administration of glucose is especially important to prevent the development of acidosis in such individuals. In diabetic patients its use should be made only with the advice and coöperation of one who is skilled in the handling of patients with that disease. Crile<sup>1</sup> has recently strongly emphasized the necessity of maintaining the liver at its normal temperature in order to keep up the normal hepatic metabolism. He makes use of diathermy for this purpose. One plate of the diathermy apparatus is placed on the lower chest on one side and the other is brought opposite the dome of the liver. The current can thus be continually applied during the operation; and he states that the temperature of the liver and the abdominal viscera can be maintained at or above the normal throughout the operation regardless of the exposure of the intestines.

Patients with chronic jaundice are particularly likely to bleed severely during and after an operation. Walters<sup>2</sup> found that of 29 patients with jaundice who died after operations on the gall bladder, 16 died of postoperative hemorrhage, whereas of 34 patients without jaundice who died only 2 deaths were due to postoperative hemorrhage. The mechanism of the production of hemorrhage in jaundice has been discussed on pages 210, 349. Following the suggestions of Lee and Vincent, Walters instituted at the Mayo Clinic the practice of giving calcium to jaundiced patients. From 5 to 10 cc. of a 10 per cent solution of calcium chloride in redistilled water is given intravenously once a day for three or four days until the coagulation time has been brought down to normal. The duration of the reduction of the coagulation time was found by Lee and Vincent to be about three days, but Walters found it to remain

<sup>1</sup> Crile, G. W.: *The Operative Management of Common-duct Stones*, *Ann. Surg.*, 1926, **84**, 411.

<sup>2</sup> Walters, W.: *Preoperative Preparation of Patients with Obstructive Jaundice*, *Surg., Gynec. and Obst.*, 1921, **33**, 651.

reduced in 1 case for fourteen days and in another eight days. We have also found the administration of calcium in these cases to be very satisfactory. Blood transfusions are also often of great assistance in reducing the coagulation time. In a later paper Walters and Parham<sup>1</sup> have extended their observations and have also emphasized the danger of uremia in association with jaundice. In any case of jaundice an operation should not be undertaken hastily. It is well to wait for a few days to see if the jaundice will subside, because an operation is always more dangerous in a jaundiced patient. In any case the patient should be studied carefully with reference to his coagulation time, the retention of a dye, such as phenoltetraiodophthalein, the non-protein nitrogen or urea nitrogen of the blood, the presence of sugar and acetone bodies in the urine, etc.

Diabetes, if coëxistent with the disease of the gall bladder should be treated before the operation by one skilled in the management of such cases.

**Incisions.**—Most of the incisions which have been proposed for operative attack upon the biliary system are portrayed in the accompanying illustrations, most of which have been taken from Kehr. (Figs. 194 and 195.) In general they speak for themselves without further description. The essential requirements of an incision for this work are: (1) That it gives proper exposure; (2) that the danger of a postoperative hernia shall be reduced to a minimum. As regards the question of exposure, it has seemed to us that because of the frequency of associated disease in other organs, especially in the right side of the abdomen, as in the appendix, the duodenum or the region of the pylorus, etc., the incision should be so placed that easy access to these other organs could be obtained. We believe that in general, because of the reasons mentioned in Chapter III regarding the pathogenesis of cholecystitis, operations for inflammations of the biliary tract should be accompanied by the removal of the appendix. We, therefore, prefer in our own work to use the incision portrayed in Fig. 196. We have not found this incision described as one in use by other surgeons, but we have no doubt that it has been used by others and perhaps by many. For that reason we do not seek to claim it as original, but we have put under it the name of one of us, merely to indicate that the incision which we prefer is different from those others which are represented in the illustrations. It begins as a vertical incision about  $\frac{3}{4}$  inch (1.5 cm.) to the right of the mid-line, and it extends downward from

<sup>1</sup> Walters, W. and Parham, D.: Renal and Hepatic Insufficiency in Obstructive Jaundice, Surg., Gynec. and Obst., 1922, **35**, 605.

a point about 1 cm. below the costal arch to a point about 1 cm. below the umbilicus. It is carried down in the same line through the anterior sheath of the rectus muscle. This muscle is not divided but is separated by blunt dissection from its attachments to the

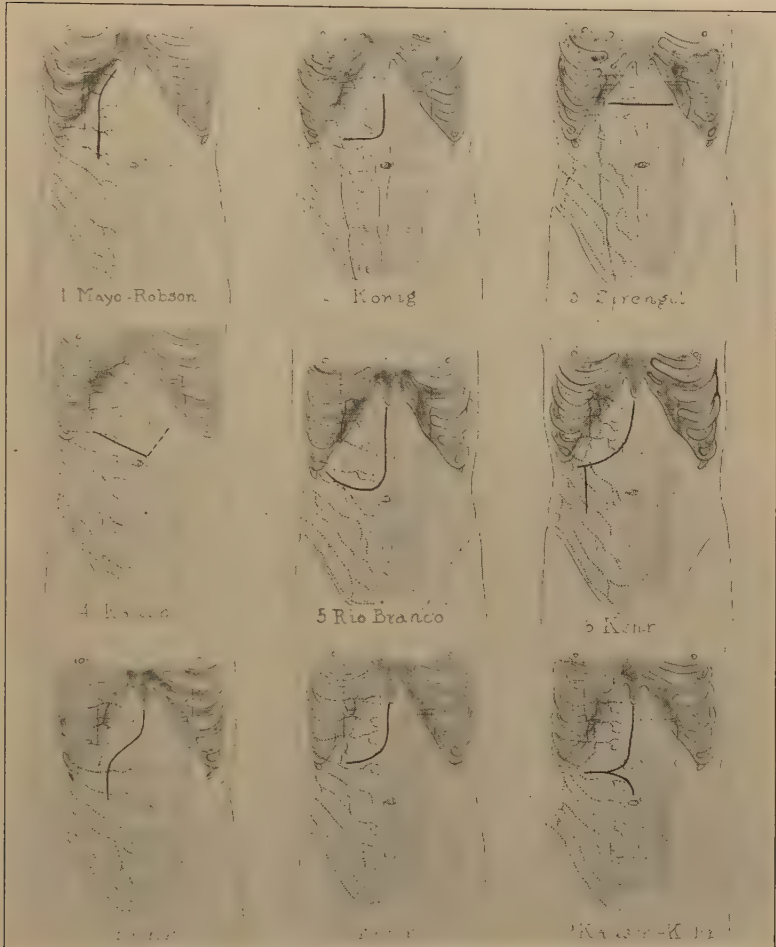


FIG. 194.—Various incisions that have been recommended for operations on biliary tract. (Modified from Kehr.)

mid-line, and the whole muscle is then retracted laterally. The posterior sheath of the rectus muscle and the parietal peritoneum are then divided in a line about corresponding to that of the incision through the anterior sheath. If sufficient exposure is not obtained



in this way the upper part of the rectus muscle is cut transversely by extending the upper angle of the incision diagonally upward to the ensiform cartilage in a manner similar to the Mayo-Robson incision, or the sheath of the rectus can be cut transversely to permit a

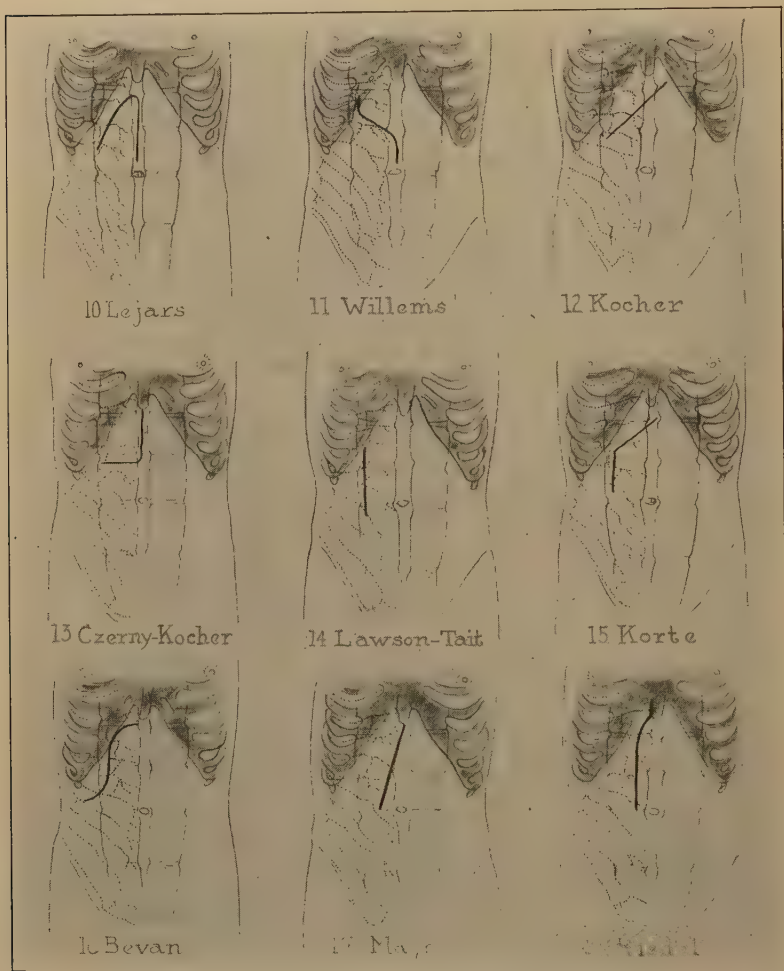


FIG. 195.—Incisions continued. (Modified from Kehr.)

greater retraction of the uncut muscle. If more exposure is desired at the lower part the vertical incision is merely extended downward. By this incision it is practically impossible to inflict injury on the nerves to the rectus muscle except perhaps at their extremities near

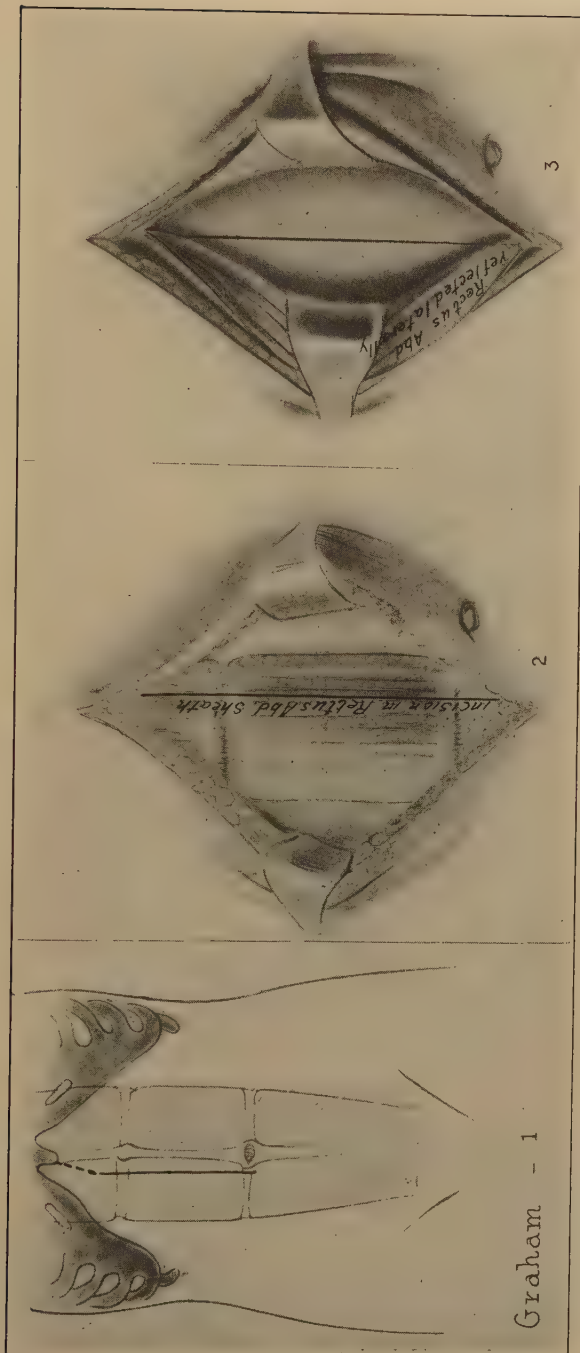


FIG. 196.—Incision preferred by authors. For description see page 402. This incision is a modification of the Kammerer incision. The incision is made close to the mid-line. The anterior sheath of the rectus muscle is split and the rectus muscle itself is retracted laterally instead of being split.

the mid-line which supply but few of the muscle fibers at most. Because of its proximity to the mid-line the incision also permits excellent exposure of the important region of the junction of the cystic with the common ducts. In closure, the intact main belly of the muscle is interposed between the two incisions in the anterior and posterior sheaths respectively. The protection afforded by the

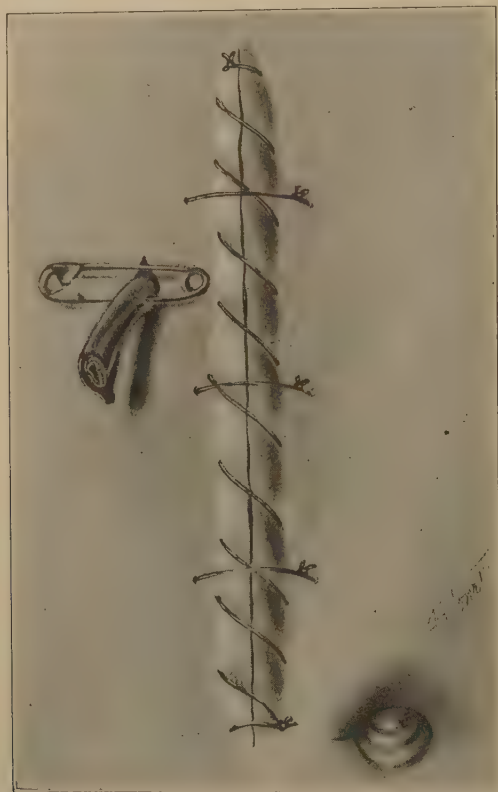


FIG. 197.—Incision closed with rubber dam drain brought out through stab wound just to the lateral aspect of the incision.

muscle in addition to the fact that its nerve supply is uninjured is added security against the development of a hernia. Drainage is secured through a stab wound to the right of the incision which is closed tightly. (Fig. 197.) In closing the anterior sheath it is our custom to use a continuous suture of No. 1 plain cat-gut reinforced by several interrupted sutures of the same material over the continuous suture. Finally about three silk-worm sutures are passed

through the skin and the anterior sheath of the muscle. These are protected by slipping over them pieces of small rubber tubing which were omitted by the artist in the drawing.

### OPERATIONS ON THE GALL BLADDER.

Operations on the gall bladder for cholecystitis whether accompanied by stones or not are chiefly of two kinds. In one the vesicle is opened and any contained stones are removed, followed by drainage through a tube. In the other kind the gall bladder is removed. The former operation is known as *cholecystostomy* and the latter *cholecystectomy*. The operation of *cholecystotomy*, in which the organ is opened and closed again without drainage, mentioned in the first paragraph of this section, is now obsolete as a therapeutic measure, although by some it is still used for the purpose of inspection of the mucous membrane of the organ at operation.

Until comparatively recently the operation of cholecystostomy, because of its greater ease of accomplishment, was the one most usually performed. At the present time, however, many more operations of cholecystectomy are performed than of cholecystostomy, at least in the larger clinics. The reason for this changed tendency is the recognition of the fact that many patients whose gall bladders have been drained later develop evidence of a recurrence of their former trouble, and in at least some cases there seems to have been indubitable evidence that gall stones have formed again in the gall bladder.

**Cholecystostomy.—Indications.**—Indications for cholecystostomy vary with different surgeons. At our hands this operation is performed only in those cases in which for various reasons it seems unwise to assume the slight additional risk of the removal of the gall bladder. Such cases are the very aged, those cases with pronounced and definite evidence of myocardial disease in which relief of pain from the presence of calculi is imperatively demanded, those with advanced renal and arterial disease, etc. In certain cases also of empyema of the gall bladder in which operation has seemed advisable, it is sometimes better to do a two-stage operation, the first stage consisting of drainage and the second stage of removal of the organ.

**Operation.**—After using the incision described above the gall bladder is inspected and palpated. It is advisable also to make a thorough examination of the rest of the abdominal cavity at this time, particularly for the presence of palpable stones in the common duct, for



lesions of the stomach, the pancreas, the appendix and in the female, the pelvic organs. If the gall bladder is distended some of its contents are removed with a syringe or a trocar, after carefully packing in gauze to prevent soiling of the abdominal cavity from a possible leakage. The organ is then seized with forceps, delivered outside the wound, and an incision is made into the fundus. Care should be exercised to prevent the escape of any bile or pus from the gall bladder into the abdominal cavity. Scoops of various sizes are then inserted into the organ through the incision for the purpose of removing any contained calculi. After collapse of the organ has occurred from discharge of its contents it is well to palpate carefully the region of the cystic duct for the presence of a possible stone impacted in the duct. It is well also to insert a finger into the gall bladder because often stones that may remain undetected by the scoop will be found in this way. If bile does not flow from the organ the search for an obstruction of the cystic duct should be continued. When, however, there is a free flow of yellow bile, a tube for drainage may be inserted. For this purpose a soft rubber tube with a lumen of about  $\frac{1}{2}$  inch (1 cm.) in diameter with a window or two cut in its side near the end is passed into the lumen. This is stitched to the wall of the gall bladder by passing a suture of No. 1 chromic catgut through both the tube and all layers of the wall. A purse-string suture of No. 1 plain catgut is then placed in the serosa and muscle layers of the gall bladder. Before the purse string is tied the edges of the incision are invaginated into the lumen of the organ. This step is facilitated by pushing the tube inward. This procedure, because the tube is sutured to the wall, carries the wall in with it. After carefully tucking in the edges of the mucosa the purse string is tied. (Fig. 198.) Some surgeons prefer to suture the gall bladder to the parietal peritoneum, but such an act seems to favor the formation of a permanent biliary fistula. For that reason we do not suture it to the abdominal wall. The tube, which is left long, is brought out through a stab wound to the right of the incision which is closed tightly in layers without drainage. If it is made to pass through the omentum on the way out, there is greater assurance of ultimate complete closure of the fistula, a fact which was shown years ago by C. H. Mayo. The tube is connected with a bottle at the side of the patient's bed, and it is our custom to allow it to remain in place until it falls out. Some surgeons prefer also to drain Morison's pouch separately by means of a small tube or a piece of rubber dam which runs from behind the gall bladder out through the same stab wound, which permits the egress of the tube that has

been placed in the gall bladder. The steps of the operation are illustrated in Fig. 198.

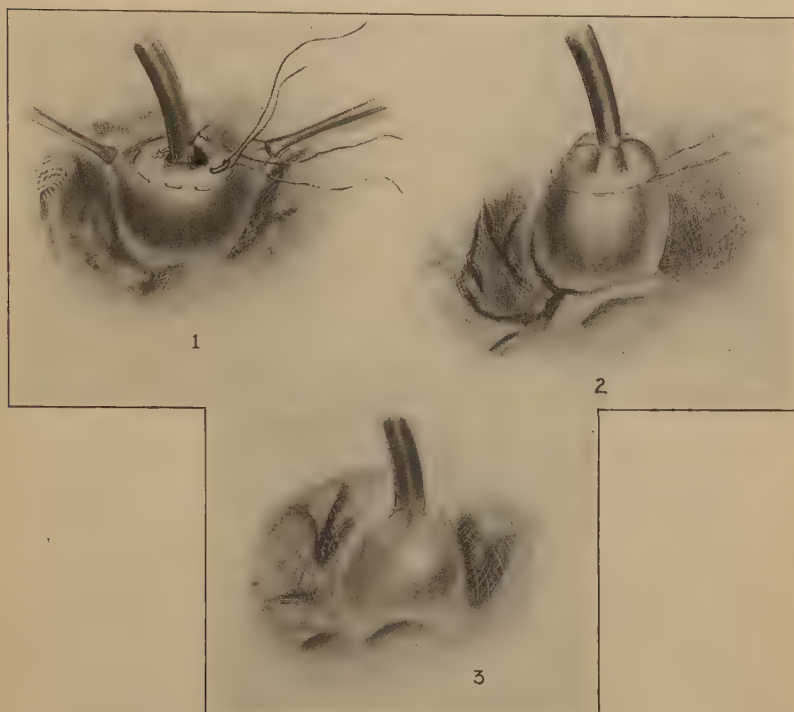


FIG. 198.—The operation of cholecystostomy in various stages. See page 407 for description.

**Cholecystectomy.**—**Indications.**—In our own work we prefer to remove the gall bladder whenever it shows definite evidence of disease. Exceptions are made in those cases in which because of the precarious condition of the patient for various reasons we believe that the slight additional risk of cholecystectomy over cholecystostomy makes the former operation unjustifiable in the particular case. In spite of acknowledged but poorly understood functions possessed by the gall bladder, the many operations of cholecystectomy which have been performed have clearly established the fact that a diseased gall bladder can be removed without unfavorable consequences, and indeed, in the majority of instances, with great improvement in the patient's condition. Whether the demonstration of seriously disturbed function, as shown for example by cholecystography without gross pathological changes will prove to be an

indication for cholecystectomy remains to be seen. The criteria of disease, as judged by gross pathological changes, have been given on page 181.

**Operation.** There are two methods of performing cholecystectomy. In one, the gall bladder is removed after first clamping the cystic artery and duct, and in the other it is removed from above downward. The former method makes the actual removal of the gall bladder nearly bloodless, and it is the method which we prefer.

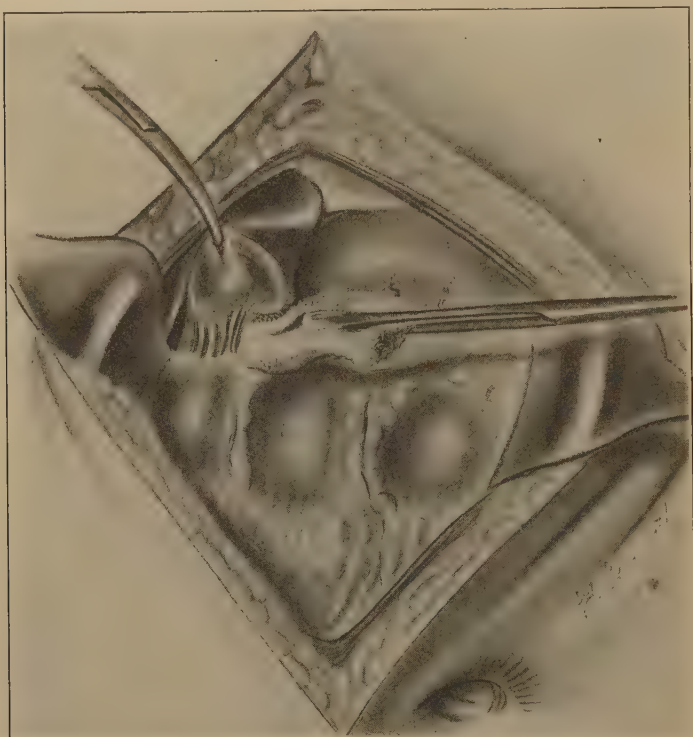


FIG. 199.—Method of separation of adhesions by use of a gauze sponge.

There are occasional cases, however, in which it seems safer and easier to remove the organ by beginning at the fundus.

In the former method the fundus of the gall bladder is seized with a forceps and pulled forward out of the wound and also up toward the patient's head in order to expose the under surface of the gall bladder and the structures around the junction of the cystic and common ducts. For this purpose Judd recommends a sponge-holding forceps. We generally employ an ordinary Kelly hemo-

static clamp. The liver is brought out of the wound as much as possible in order to facilitate exposure of the ducts. To accomplish this, various procedures have been recommended. Moynihan has advised rotation of the liver slightly. Masson<sup>1</sup> has proposed the insertion of a pack between the liver and diaphragm. If adhesions are present on the under surface of the gall bladder they are most easily separated in the average case by means of a gauze sponge in a forceps as shown in Fig. 199. The region of the neck of the gall bladder is seized with another forceps and also pulled upward. This procedure usually affords adequate exposure of the hepato-duodenal ligament. To obtain exposure of the ducts themselves the

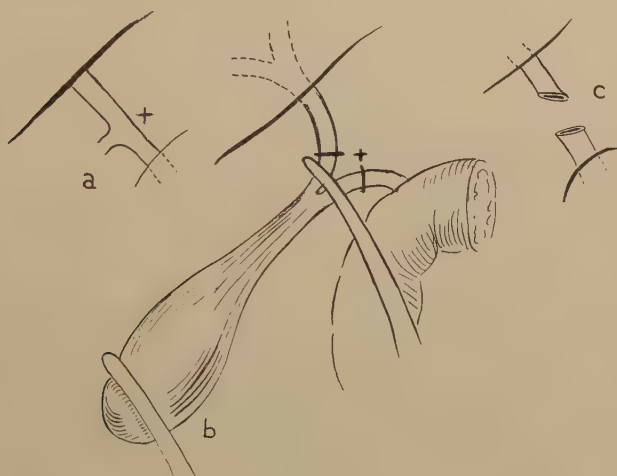


FIG. 200.—A frequent cause of injury to the common-bile duct. If too much traction is made upon the gall bladder the common duct may be pulled out at such an angle that it will be clamped and completely divided by mistake.

tissues around them are carefully divided by blunt dissection in the direction of the common duct. Bluntly pointed scissors or hemostatic forceps are inserted into the tissues and then spread open. This act is repeated until satisfactory exposure of the ducts is accomplished. It is essential that the junction of the cystic with the common hepatic ducts be clearly seen before the cystic duct is cut across. Only by that safeguard can the occasional accidental severing of the hepatic duct be avoided. A common reason for the occurrence of this serious accident is portrayed in Fig. 200, in which it is seen how traction on the cystic duct may pull up the common

<sup>1</sup> Masson, J. C.: Exposure in Gall-bladder Surgery, *Ann. Surg.*, 1919, **69**, 422.



duct in such a way that when a clamp is applied supposedly to the cystic duct alone it grasps also the common hepatic duct. In exceptional cases, because of peculiarities in the arrangement of the ducts, it is impossible to see the junction of the cystic with the common hepatic duct. Indeed in some cases, as was shown in Chapter I, the two ducts do not unite until low down in their courses. In all of these exceptional cases, in order to avoid injury to the hepatic duct, it is essential that the cystic duct be plainly seen to begin at the gall bladder. A procedure which will often be found useful in the identification of the ducts is the use of a curved Cameron light. If the light is inserted behind the hepato-duodenal ligament all the duct and even the cystic artery will often be disclosed by this method of transillumination. When the duct has been satisfactorily exposed, two clamps are placed on it and the duct is severed between them. For this purpose special right-angled clamps may be used but the ordinary curved Kelly hemostatic forceps are satisfactory. It is well to touch the stump of the cystic duct with a drop of carbolic acid in order to disinfect it. When the duct is severed, only one lumen should show in the cross-section. If there are two, it is a clear indication that an hepatic duct also has been cut across, and steps should be taken at once to repair the injury in accordance with the methods described later on page 438. It is not necessary that the entire cystic duct should be removed flush with the common hepatic duct. In the interests of safety it is wise to leave enough of the cystic duct to minimize the danger of later cicatricial contraction of the common duct. In those cases in which it is difficult or impossible to tell with certainty the location of the common duct, some help may be obtained by puncturing the supposed duct with an hypodermic needle and syringe to see if clear yellow bile is obtained. Finally also in all cases of doubt it is much wiser to leave a small portion of the gall bladder than to run the risk of injuring the hepatic or common ducts. (Figs. 201, 202, 203, 204 and 205.)

The cystic artery may often be grasped in the same clamp which is applied to the cystic duct, but generally we prefer to catch it separately. In many cases it can be seen pulsating to the right of the cystic duct and slightly posterior to it. The severed end of the cystic duct and the gall bladder are lifted upward by gentle traction on the forceps; and, if the artery has not already been seen and clamped, another forceps is applied behind and close to the gall bladder to seize any vessels in this region. Care is taken to keep close to the gall bladder in order to avoid the possibility of clamping an hepatic duct. The traction on the vesicle end of the cystic



FIG. 201.—The operation of cholecystectomy after first exposing and isolating the cystic duct.



FIG. 202.—The operation of cholecystectomy continued. The cystic duct, after being exposed, is doubly clamped and is cut between the clamps.

duct tends to minimize the danger of injury to the hepatic duct. If the cystic artery is not caught in a clamp before cutting it, or if an unrecognized accessory artery is present, hemorrhage may occur copiously enough to obscure the field. In such an event it is very essential that no blind and promiscuous attempts to catch the bleeding vessel should be made because by so doing there is great danger of accidentally clamping the hepatic duct. A much

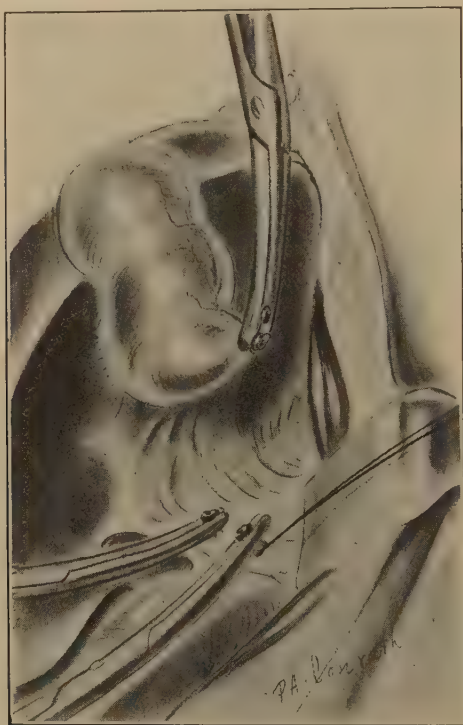


FIG. 203.—The operation of cholecystectomy continued. Usually the cystic artery is found in the position indicated in the illustration. It is clamped and divided and removal of the gall bladder is then begun.

safer procedure is to press firmly with a sponge in the direction of the bleeding for a few minutes. Then after gently removing the sponge the bleeding vessel can often be seen and safely clamped. If this method of securing hemostasis is not successful the entire region should be packed tightly for a few minutes with a large hot gauze pack which is carefully removed in about five minutes. With the removal of the pack the bleeding will usually begin again and the vessel can generally be recognized. Another helpful procedure is to

insert the left index finger into the foramen of Winslow and to squeeze the hepatic artery between the finger and thumb. This will control the bleeding from the cystic artery which can be recognized when the pressure on the hepatic artery is diminished again. Any serious bleeding should always be controlled before the gall bladder is removed and before the clamp on the stump of the cystic duct is taken off, because traction on these two structures is of very great assistance in the recognition of the source of the hemorrhage.

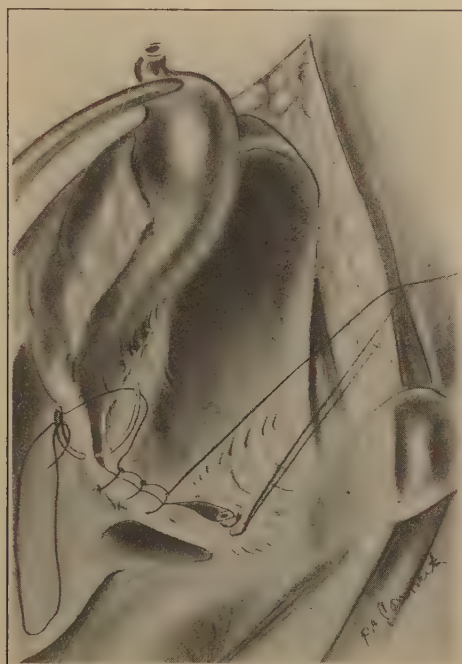


FIG. 204.—The operation of cholecystectomy continued. The removal of the gall bladder is now nearly complete and the bed of the liver is being covered with peritoneum. This may be begun at the lower end or at the upper end as shown in Fig. 205.

After the clamping and cutting of the cystic duct and artery one can proceed with the removal of the gall bladder. In the course of cutting of the attachments of the organ at its lower end one occasionally encounters an accessory duct running to the cystic duct from either the liver or from one of the hepatic ducts. If such a duct is seen it should be ligated to avoid the possibility of a later escape of bile from its cut end. In most cases, as the gall bladder is stripped upward from its attachments, a portion of the peritoneal coat can be left on either side of the bed which may be used to cover the raw



surface of the liver. But in other cases the peritoneum becomes stripped off the liver so that there is not a sufficient amount left with which to form flaps to cover the raw surface. If there is a considerable amount of oozing from the raw surface of the liver it can be controlled by tightly applying a hot pack to the surface for a few minutes. The raw surface of the liver is then sutured across. If peritoneal flaps have been obtained from the gall bladder an excel-

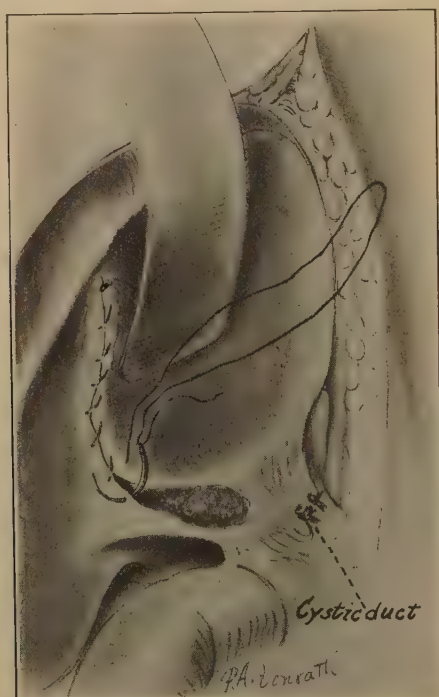


FIG. 205.—The gall bladder has been removed and the raw surface on the liver is being covered with peritoneum. Sometimes it is not possible to cover the raw surface so well as is indicated in the illustration. In such cases mattress sutures can be placed through the liver to bring the edges together.

lent covering of the raw surface can be accomplished. If not, it is usually necessary to pass the sutures through the liver substance, and sometimes it may even be necessary to apply mattress sutures to bring the edges of the raw area together. Some surgeons prefer to bury the stumps of the cystic duct and of the artery beneath the peritoneal flaps. Our own practice, however, is not to do this both because we feel that there may be an added risk of injury to the hepatic ducts in the suturing and also because we feel that if a sub-

sequent leakage of bile should occur from the cystic duct it is better to have it come out through a drainage track than to dissect up the flaps covering the raw surface of the liver. We drain almost all cases; and for this purpose we prefer a small roll of rubber dam which is passed from the region of the stump of the cystic duct through a stab wound just to the right of the incision. The drain is removed after two days unless there is a discharge of bile, in



FIG. 206.—Another method of performing cholecystectomy by beginning at the fundus of the gall bladder instead of at the cystic duct. (Modified from Kehr.)

which case it is permitted to remain for a longer time. (Figs. 206, 207 and 208.)

An interesting example of the effects of seepage of bile between the liver and the peritoneal flaps covering its raw surface after cholecystectomy is given by Polya.<sup>1</sup> A week after the cholecystectomy the patient became jaundiced with clay-colored stools, with enlarged liver and with fever. Eight months later Polya found a thin-walled

<sup>1</sup> Polya, E.: Gallencyste nach idealer Cholecystektomie, *Centralbl. f. Chir.*, 1925, 52, 2341.

cyst in the region of the former bed of the gall bladder. The cyst was drained, and 200 cc. of bile escaped the first day. Improvement was rapid from that time, and twenty months later when seen again the patient was in good health.

The operation known as "ideal cholecystectomy" is performed by some surgeons in which no drainage is carried out after the removal of the gall bladder. It is the opinion of those who favor this operation that relatively few or no adhesions occur if drainage is omitted.

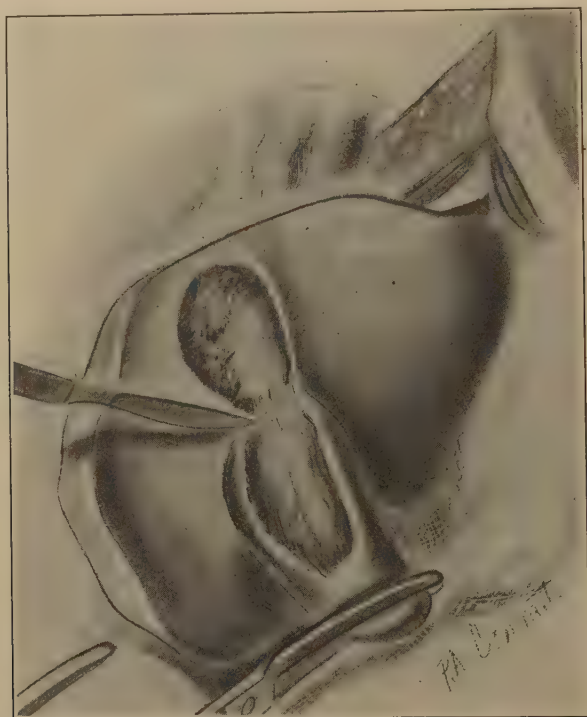


FIG. 207.—The same operation as Fig. 206, showing the separation of the gall bladder from the liver. (Modified from Kehr.)

In certain cases, however, postoperative escape of bile into the peritoneal cavity is inevitable and it may have disastrous results unless an outlet to the exterior is provided. For that reason we prefer to drain all cases. The seepage of bile may occur from unrecognized accessory ducts which are cut across during the removal of the gall bladder.

**Operative Mortality.**—In recent years the published statistics from various clinics have always shown a higher mortality for the opera-

tion of cholecystostomy than for that of cholecystectomy. It is incorrect, however, to infer from this fact that actually the simple surgical drainage of the gall bladder is a more formidable procedure than its removal. The true explanation of the apparent paradox lies in the fact that in the majority of instances the operation of cholecystostomy is performed only in those cases in which the risk is bad. Judd and Parker,<sup>1</sup> in a recent article have discussed the mortality after operations of cholecystostomy and cholecystectomy

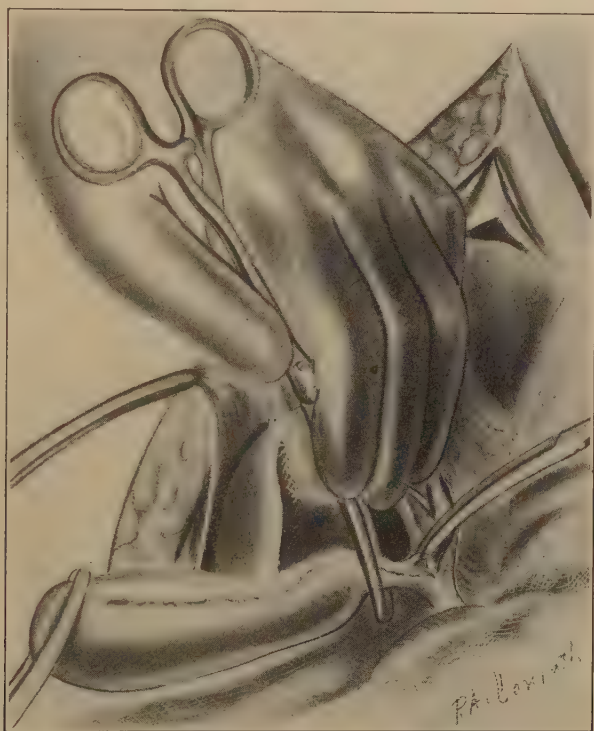


FIG. 208.—The same operation continued showing the exposure of the cystic duct.

respectively at the Mayo Clinic. In 49 cases of cholecystostomy there was an operative mortality of 7.2 per cent and in 845 cases of cholecystectomy the mortality was 1.4 per cent. In Blalock's analysis of the results at the Johns Hopkins Hospital the mortality percentages were as follows: In 735 operations of all kinds on the biliary tract, there was a mortality in 9.5 per cent of the cases,

<sup>1</sup> Judd, E. S. and Parker, B. R.: Mortality following Operations on the Biliary Tract, Pancreas and Liver, *Ann. Surg.*, 1926, **84**, 419.



although this mortality percentage was very much lower in recent years. Of the deaths following operations on the gall bladder alone, 39 per cent occurred after cholecystectomy and 61 per cent after cholecystostomy.

In our own experience in the last 309 cases of cholecystectomy for both acute and chronic cholecystitis, with and without stones, there have been 9 deaths, a mortality of 2.8 per cent. During the same time there have been 11 cases of cholecystostomy with 2 deaths, a mortality of 18 per cent. The reason for this marked difference in the operative mortality has been due solely to the fact that cholecystostomy has been performed only in those cases which were the worst risks.

The causes of death in the above cases have been as follows:

*Cholecystectomy.*

Myocarditis and acute cardiac failure . . . . .	3 cases.
Pneumonia . . . . .	2 cases.
Subdiaphragmatic abscess with pneumonia . . . . .	1 case.
Localized peritonitis with pyemia . . . . .	1 case.
Unknown; no autopsy . . . . .	2 cases.

*Cholecystostomy.*

Carcinoma of bile-ducts with metastases . . . . .	1 case.
Pylephlebitis with multiple abscesses of liver . . . . .	1 case.

It is an interesting fact that women withstand operations on the biliary tract better than men. In our own series of operations of all kinds on the biliary tract, 51.4 per cent of all deaths were in males, although there were 2.6 times as many female patients as males. This indicates that, in general, the operative risk to a male patient is about three times as great as in a female. Blalock found a similar proportion in his cases, namely, that although two-thirds of the patients in his series were females only 44 per cent of the fatalities were in that sex.

**Cholecystostomy Versus Cholecystectomy.**—The indications for cholecystostomy and cholecystectomy respectively differ very widely among surgeons. By far the majority favor cholecystectomy in the average case. Palmer<sup>1</sup> in 1925 compiled answers received from 38 prominent surgeons regarding their positions on this question as follows:

TYPE OF OPERATION PERFORMED NOW AS COMPARED WITH TWO YEARS AGO.

Performing more cholecystectomies today . . . . .	17 (44.8 per cent).
Performing more cholecystostomies today . . . . .	6 (15.8 per cent).
No change . . . . .	15 (39.4 per cent).
Percentage of secondary operations after cholecystectomy about	2 per cent.
Percentage of secondary operations after cholecystostomy about	15 per cent.

<sup>1</sup> Palmer, D. W.: Rationale of Gall-bladder Therapeusis, Ohio State Med. Jour., 1925, 21, 309.

The reason for favoring cholecystectomy over simple drainage is of course that by removing the organ it is felt that there is less likelihood of a recurrence of the trouble. It is possible that as experience with cholecystography increases, it may be found feasible merely to remove calculi and to allow the gall bladder to remain if it has been shown to have a good concentrating function. At the present time, however, there is not sufficient experience at hand to justify this practice, in our opinion. The whole question of drainage *versus* removal of the organ is concerned also with the much larger questions of how often cholecystitis recovers spontaneously and also of how much drainage of its lumen is a factor in aiding this spontaneous recovery. As regards the first of these two questions it is reasonable to assume, and there is some clinical experience to support the assumption, that cholecystitis occasionally does recover spontaneously, but it is impossible at present to state with any degree of accuracy how often this result occurs. Clinical impressions are almost unanimous in the opinion that the majority of cases of cholecystitis do not recover spontaneously but become chronic and persistent. As regards the second question one can also say that drainage undoubtedly often results in recovery but that in many cases it certainly does not. Statistical information on this subject that is available is not entirely satisfactory. Stanton,<sup>1</sup> however, in 1911 found only 46 per cent of clinical cures in a series of 99 cases, in 92 of which cholecystostomy had been performed. Also Blalock, in the Johns Hopkins Hospital series, found that of those cases which had a recurrence of symptoms 79 per cent had had a cholecystostomy. In a more recent study Cave has shown in an analysis of cases from the Roosevelt Hospital that 86.1 per cent of the cholecystectomy cases were free from symptoms and that 56 per cent of the cholecystostomy cases had reoperations.

**The Relief of Symptoms after Cholecystectomy.**—The recurrence or persistence of symptoms following the operation of cholecystostomy has already been discussed above. Since it is reasonable to suppose that the complete removal of the gall bladder should yield a much higher proportion of satisfactory results, the general nature of the results will be discussed. As a rule, the most nearly complete relief of symptoms after cholecystectomy is obtained in those cases in which stones are present. Müller,<sup>2</sup> for example, has found in his

<sup>1</sup> Stanton, E. M.: End-results in Gall-bladder Surgery, Jour. Am. Med. Assn., 1911, 57, 441.

<sup>2</sup> Müller, G. P.: The Noncalculous Gall Bladder, Jour. Am. Med. Assn., 1927, 89, 786.

series that 84.4 per cent of the stone cases were clinically cured but only 70 per cent of the non-calculous group. He quotes Whipple also as having found that 89.4 per cent of his calculous cases and only 76.6 per cent of his non-calculous cases were relieved of their symptoms by cholecystectomy. Judd<sup>1</sup> has carefully analyzed the postoperative results of 300 cases of cholecystitis in which cholecystectomy was performed in an effort to compare the results in the calculous with the non-calculous cases. In general, he found that by far the best results were obtained in those cases in which the classical symptoms of gall-bladder disease were present whether accompanied by stones or not. He has divided his cases into five groups. Group I has the least pathological evidence of disease, and in many cases of this group the clinical history rather than recognizable lesions constituted the grounds for operation. In this group there were 64 per cent of good results, 20 per cent of fair results and 13 per cent of poor results. Group II comprised the cases of strawberry gall bladder and differed from Group I only in the fact that the gall bladders in this group had the yellowish lipoidal deposits in the mucous membrane. In this group the results were much the same as in Group I. They were good in 67.4 per cent, fair in 19.6 per cent, and poor in 8.7 per cent. Group III comprised the more severe grades of cholecystitis without stones. In this group the results were good in 70 per cent, fair in 18 per cent, and poor in 6 per cent of the cases. Group IV comprised the strawberry gall bladders with stones present. The results were good in 87.8 per cent, fair in 8.2 per cent, and poor in 2 per cent of the cases. The fifth group consisted of the most severe cases of cholecystitis with stones. In this group the results were good in 81.3 per cent, fair in 12.5 per cent, and poor in 2 per cent of the cases.

Possible factors in the persistence of symptoms are in general of two kinds, of which one is perhaps the presence of residual infection in the liver, pancreas, or appendix which does not undergo resolution. Other factors of perhaps greater importance are errors in diagnosis and incomplete diagnosis. The symptoms of spastic constipation or of mucous colitis, for example, may frequently simulate those of a less severe grade of cholecystitis. If the gall bladder is removed in such a case, even if it shows some evidence of old inflammation, the symptoms of abdominal discomfort may still continue for the simple reason that the gall bladder may have played only a very minor rôle in their production. There are of course many other

<sup>1</sup> Judd, E. S.: *Clinical versus Pathological Cholecystitis*, Collected Papers of the Mayo Clinic, 1925, 17, 152.

possible sources of error, as, for example, osteo-arthritis of the spine. The mere fact that the gall bladder shows evidence that it has once been the site of disease, as for example by the presence of adhesions and scar tissue, does not necessarily imply that it is giving rise to symptoms. In the case of the gall bladder there has perhaps been too great a tendency to think that the mere presence of adhesions, thickening, etc., must imply the coëxistence of symptoms caused by these changes, although actually they may only indicate the healing of a former inflammation and not necessarily the existence of any active inflammation. In the case of other organs we do not carry out the same sort of reasoning. For example in the case of a painful finger we do not at once incriminate an old scar in the skin which may represent an old infection which has healed years ago. But rather we think of other possibilities such as an unrelated, recently acquired infection of the soft parts, a recently acquired arthritis, etc. Similarly in the case of a scar in the duodenum we do not rush to the conclusion that it is the cause of symptoms because we know that often it is merely an indication that an ulcer, formerly existing, has healed. Of more importance than the mere recognition of evidences of old inflammation in the gall bladder is the determination of whether such changes actually cause symptoms. Heretofore, in order to determine these matters, we have had to rely merely on the findings at operation and the subsequent experiences of patients who have been submitted to operative procedures. We have had no opportunities for an examination which would permit us to judge of the effect of such changes on the function of the organ, such as we have had, for example, in the case of lesions of the stomach and intestine. With the advent of cholecystography, however, a method has been presented which permits one to study at least the functions of concentration and time of emptying, in a manner similar to the study of the functions of the intestinal tract by means of the barium meal. We venture to express the hope, therefore, that the intelligent use of cholecystography may provide a method of determining the source of symptoms in a doubtful case, which when combined with the pathological findings may prove to be of greater value than the latter alone. It also seems to us within the bounds of reason to suppose that the gall bladder may, like other organs, have a disturbance of its function without definite recognizable pathological changes, and that this disturbed function may be productive of symptoms. Cholecystography when properly employed may serve to detect these cases of disturbed function.



On this basis Olch<sup>1</sup> studied 100 consecutive patients who had shown pathological gall bladders by cholecystography after intravenous injections and had had cholecystectomies at the Barnes Hospital. The patients were followed up after operation, and all were relieved of their symptoms. The shortest period of time in any case between the operation and the interview or the correspondence with the patient was ten months. The cases were grouped as follows according to the pathological condition of the gall bladder:

Group.	No. of cases.	Gall stones.	Condition of gall bladder.
A . . . . .	33	Present	Thick, scarred.
B . . . . .	8	Absent	Same as Group A.
C . . . . .	7	Present	Thin-walled, translucent to slightly thickened.
D . . . . .	52	Absent	Same as Group C.

*Group A.*—Grossly these 33 gall bladders were thick and fibrous, some reduced to a mass of scar tissue. All contained stones. Microscopically, there was marked round-cell infiltration throughout the whole thick wall. The mucosal epithelium was intact in many cases, and in others it was missing in places. Buried in the scarred wall were small, gland-like areas of mucosal epithelium, separated from the lining mucosa by the sclerosing inflammatory process. When a small piece of liver tissue was removed for examination it invariably showed lymphocytic infiltration of the periportal areas. Twenty-two of these 33 patients gave the definite clinical history and symptoms usually attributed to cholecystic disease. The remaining eleven gave indefinite symptoms.

*Group B.*—This group differs from the preceding one only in the fact that no stones were found in the gall bladder. Five of these 8 cases gave a definite history and the other 3 did not.

*Group C.*—This is composed of 7 cases, 4 of which gave definite symptoms and the remaining 3 did not. Grossly, the gall bladders removed from these patients were but slightly thickened and the mucosæ intact. They contained gall stones, which were not suspected in 5 of the cases until the gall bladders were opened. This was because the latter were so distended with bile that the few small stones could not be palpated. None of these stones were recognized as such in the cholecystograms.

<sup>1</sup> Olch, I. Y.: Chronic Cholecystitis: An Analysis of 100 Consecutive Cases Diagnosed with Cholecystography and Treated by Cholecystectomy, in which the End-results were Investigated, *Am. Jour. Med. Sci.*, 1927, **173**, 368.

## PLATE VIII



Colored Drawing Made at Operation on a Patient Whose Gall-Bladder was Not Visualized in the Cholecystographic Films.

At operation a nearly normal gall bladder was disclosed except for the presence of a few adhesions on the under surface. Despite the slight pathology present this gall bladder very clearly had a disturbance of function sufficient to result in no visualization of the gall bladder after intravenous injection of phenoltetraiodophthalein. Cholecystectomy was performed and the patient's symptoms, chiefly those of dyspepsia with slight pain, have been completely relieved for two years. This kind of case has been a common one in our experience. We believe that the decision to remove the gall bladder should be determined not so much by a slight pathological change as by the additional fact as to whether or not there is a marked functional disturbance of the organ. Cholecystography gives us a means of determining the only two functions known to be possessed by the gall bladder.



*Group D.*—Only 18 of these 52 patients gave symptoms or histories which definitely pointed to cholecystic disease. The remaining 34, or 65 per cent, gave only indefinite histories with complaints of dyspepsia, eructations, epigastric pain relieved by soda and simulating gastric or duodenal ulcer, vague, diffuse abdominal pain, etc. Such a history in addition to cholecystographic evidence of abnormality, was our justification for operation. In some of these cases the cholecystograms showed no shadow at all, while in many there was a faintness of shadow which was interpreted as denoting an impaired concentrating ability. At laparotomy, in these 52 cases the gall bladders *in situ* were found to be thin, distended and characteristically bluish. Many were slightly or moderately thickened, and others showed no appreciable thickening. Often on the surface were a few adhesions, binding the organ sometimes to the duodenum, or omentum, or pylorus, or more densely to the liver. (Plate VIII.) After removal these gall bladders were found to have thin or only slightly thickened walls and intact mucosæ. In 10 of the 52 cases the yellow deposits of cholesterol on the mucosa characteristic of the strawberry gall bladder were present. Microscopically, the mucosa in every case was intact. Deep beneath it, in the muscle layer and extending to the serosal surface, or to the area adjacent to the liver, there was, in all but 8 cases, diffuse lymphocytic infiltration, in no case extensive, but usually slight to moderate. In the small piece of liver routinely excised there was always found infiltration of the periportal spaces with lymphocytes, varying from very slight to moderate in degree.

This high percentage of successful results (100 per cent) after cholecystectomy found by Olch is of course surprising. As explanations of the apparent discrepancy between his findings and those of others should be mentioned, first that the diagnosis of abnormality of the gall bladder in his series rested not only upon clinical symptoms and the findings disclosed at operation but also upon cholecystographic findings as well. We feel this to be a very important point since by means of cholecystography we can more definitely incriminate the gall bladder as a source of the patient's symptoms. Also, it should be stated that after all, 100 cases is a small series and that in a larger one an equally successful number of results could hardly be expected. It might also be stated that it is our routine practice to remove the appendix at the same operation as the cholecystectomy.



### TREATMENT OF TUMORS OF THE GALL BLADDER.

The benign tumors of the gall bladder, most of which are papillomata or adenomata, are best treated by cholecystectomy. These tumors are not often recognized until after the excised organ has been opened and examined, and for that reason alone no other treatment than the removal of the organ could be expected to be satisfactory.

Carcinoma of the gall bladder is nearly always associated with calculi, and therefore in the early stages, before perhaps a gross diagnosis could be made, the condition falls into the category which demands cholecystectomy any way, according to the opinion of most surgeons. When the case is sufficiently advanced to be recognizable to the naked eye it is doubtful how much good can be accomplished by cholecystectomy. If the gall bladder can be removed without too much risk, obviously its removal would seem to be indicated. One of the chief difficulties as regards a permanent cure is the frequency of metastases in the liver. Some of the earlier surgeons were bold enough to remove a large portion of the liver with the gall bladder in such cases, but the results did not seem to justify so radical an undertaking. We have seen no modern reports of such cases. Moreover, we know of no published results which seem to offer much hope of a clinical cure of carcinoma of the gall bladder by the operation of cholecystectomy.

### TREATMENT OF INJURIES OF THE GALL BLADDER.

Injuries of the gall bladder resulting in the escape of bile are usually best treated by cholecystectomy. Small tears of an otherwise normal organ can be merely closed. One of the most important points in the treatment of all injuries of the biliary tract is the removal of extravasated bile from the peritoneal cavity. It is important also to search for evidences of injury to other abdominal viscera, particularly for tears in the liver. If extensive intra-abdominal hemorrhage has occurred a blood transfusion should be given.

### TREATMENT OF CONGENITAL OBLITERATION OF THE BILE-DUCTS.

In most cases of this condition nothing can be accomplished by treatment. In those cases, however, in which the obliteration is

at the lower end of the common duct temporary relief can sometimes be gained by anastomosing either the gall bladder or the upper part of the common duct to the duodenum or stomach. These operations are known respectively under the names of *cholecystoduodenostomy* and *cholecystogastrostomy*. They are described in detail on page 442. As a rule they are of temporary value in diminishing the jaundice but sooner or later the patients have succumbed as a result of severe infection of the liver and of the bile-ducts. Some cases have apparently recovered spontaneously, as if perhaps the hepatitis and cholangitis which many believe responsible for the condition had subsided before the obstruction of the ducts had become complete and final. Rolleston suggests that unless syphilis has been excluded antiluetic treatment should be tried. Holmes<sup>1</sup> has stated that in 16 per cent of all reported cases surgical relief was theoretically possible. For this reason an exploratory laparotomy would seem to be indicated in all cases.

#### TREATMENT OF CONGENITAL CYSTS OF THE EXTRA-HEPATIC BILE-DUCTS.

McWhorter, whose extensive review of this whole subject has already been cited on page 195, obtained a successful result in his case by performing a side-to-side anastomosis of the hepatic duct with the duodenum about 10 cm. from the pylorus. The stoma of the anastomosis was about 2 cm. long. The sac and the gall bladder were then removed. One year later the patient was well and was doing her own housework. McWhorter states that in the reported cases there was a low mortality only in the cases in which drainage was established into the intestine at the first operation. However, the opening must be adequate or contraction and a recurrence of the obstruction may result, requiring another operation. Nine of 48 patients reviewed by McWhorter may be considered as cured; and all of these had a permanent stoma made between the bile-duct and the intestine.

#### TREATMENT OF STONES IN THE DUCTS.

When a stone is found in the cystic duct three possibilities of treatment are offered: (1) Pushing it back into the gall bladder and then removing it either by cholecystostomy or cholecystectomy;

<sup>1</sup> Holmes, J. B.: Congenital Obliteration of the Bile-ducts, Johns Hopkins Hosp. Rep., 1919, 18, 75.

(2) incising the duct and removing the stone; (3) removal of the gall bladder and cystic duct from a point beyond the stone so that all will be removed together. Stones in the cystic duct are usually accompanied also by stones in the gall bladder; and even when no other stones are present in the gall bladder that organ is usually diseased. For these reasons we believe that the most satisfactory treatment is cholecystectomy including the cystic duct well beyond the stone. In some cases a stone is found impacted tightly in the cystic duct right at its confluence with the common hepatic duct. Under such circumstances it is impossible to carry out the procedure just recommended without great danger to the common duct. Accordingly, when confronted with such conditions, we prefer to incise the duct to remove the stone and then to perform a cholecystectomy. Or Delangière's plan may be followed which consists of incising the gall bladder and continuing the incision downward, splitting the cystic duct until the stone is exposed. Small stones in the cystic duct may easily be overlooked. It is a fairly common surgical experience to find a small stone or two in the duct after removing a gall bladder which contains numerous small stones. For this reason it is highly advisable after performing cholecystectomy to examine very carefully the stump of the cystic duct for the presence of a possible stone and to remove any that are found.

The treatment of a stone in the common duct differs according to whether it is in the supraduodenal portion of the duct, behind the duodenum, or lodged in the biliary papilla. If it is in the supraduodenal portion it can usually be detected by palpating it between the thumb and index finger when the latter is in the foramen of Winslow. Many stones can be moved for a distance of about 1 or 2 inches along the duct, but others are fixed in their positions. After carefully walling off the peritoneal cavity with gauze to prevent leakage of bile the portion of the common duct which contains the stone is firmly seized between the thumb and finger of the left hand, and a longitudinal incision is made in the duct immediately over the stone. A suture is then placed through the entire thickness of the wall of the duct on each side of the incision for the purpose of steadying it. The stone can then frequently be extruded through the incision by gently pushing forward with the finger which is behind the duct. If this is not successful it can be grasped with a small forceps and extracted in that manner. (Figs. 209 and 210.) After removal of the stone the duct should be thoroughly examined for the possible presence of other stones. To accomplish this examination a finger should be inserted into the duct both upward

and downward if the latter is sufficiently dilated. When the finger is withdrawn suddenly it acts like a piston and results sometimes in the suction of other stones out of the duct. Probes should also be passed both upward and downward. It is important to examine in this way both the right and left hepatic ducts and to



FIG. 209.—Removal of stone from the common duct. The index finger of the left hand is inserted into the foramen of Winslow lifting the common duct forward. A longitudinal incision is then made into the duct over the stone.

pass the probe down the common duct into the duodenum. It is necessary to use a probe of fairly large caliber for this purpose, because a small one may slip past a stone without detecting it. Small scoops are often used more advantageously than probes. In the majority of cases a single stone is present in the duct, but in



many instances there are multiple stones. Also in some cases the whole duct system is plugged with a soft mass which resembles putty in appearance. This is largely cholesterol in composition. As much of it as possible should be removed both for the purpose of relieving the obstruction of the ducts and to minimize the later reformation of stones. To accomplish its removal scoops are necessary.



FIG. 210.—After opening the duct the stone is removed with a forceps.

In most cases of complete obstruction of the common duct with jaundice there is an immediate escape of yellow bile as soon as the stone has been removed from the duct. When this occurs it is an indication that the obstruction has been removed, although it does not indicate that all stones have been removed, some of which may be too small to cause obstruction. Sometimes, however, it

happens that instead of yellow bile a mucoid colorless fluid escapes. This is the so-called "white bile." It is chiefly a secretion of the ducts themselves, and its presence indicates either that bile is no longer being formed or that its passage downward from the liver is still blocked. In most instances it signifies a very severely damaged liver, but it is gratifying that often after the removal of back pressure upon the liver by drainage a flow of yellow bile will appear. In cases of this kind the general supportive measures, particularly the administration of glucose, as mentioned elsewhere are strongly indicated. The change from white bile to yellow occasionally occurs even before the operation is completed, but sometimes no yellow bile is seen issuing from the drain until a day or two after the operation.

It is the consensus of opinion that most, if not all, cases of common-duct stone should be drained; and we agree with this opinion. This is the operation of *choledochostomy*. For this purpose rubber catheters are admirably suited, although ordinary rubber tubes will sometimes suffice. In general, the tube is placed upward into the common hepatic duct or into the right or left hepatic ducts. The purpose of placing the tube in such a position is to facilitate the drainage of bile from the liver and also to provide an easy outlet for any small overlooked stones in the hepatic ducts. McArthur, however, has made the important suggestion of inserting the tube downward into the duodenum, at least in certain cases, so that postoperatively fluids may be conveniently administered directly into the duodenum. In any event, regardless of the direction of the tube, we prefer to suture it in place. A suture of No. 1 plain catgut is passed through the wall of the duct and through the tube. After a few days the catgut has become sufficiently dissolved to permit loosening of the tube. We prefer also to close the walls of the incised portion of the duct over the tube in order to prevent leakage of bile around the tube. We see no advantage in inserting another drain down to the common duct, as some advise, because the catheter issuing from the duct will form a track to the outside along which secretions may escape in just the same manner as any extra drain which may be used. We continue drainage as long as the tube remains in place. After it has fallen out we permit the wound to close spontaneously. We do not believe there is any advantage to be gained in attempts to prolong the drainage for many weeks or months, as some surgeons have advocated. Any tube is a foreign body, and it is not desirable to have a foreign body in contact with an inflamed surface for a longer time than is necessary. In the case

of a structure like the common duct the prolonged presence of a tube may do enough damage to cause a stricture later. Also it is not to be thought that drainage of bile ceases when the tube is removed. Drainage continues spontaneously through the duct into the duodenum. Because of this fact some surgeons prefer not to drain the duct at all but to close it up tightly after removing the stones and then to pass a drain merely to the duct to provide for any possible leakage. Crile<sup>1</sup> is one of those who prefer not to drain the common duct. He warns also against the unnecessary injury of nerve fibers on the duct; and he recommends wide blocking of the area with novocaine.

In some cases unusual difficulties present themselves in removing stones from the common duct. Sometimes the foramen of Winslow is obliterated by adhesions so that the finger cannot be inserted into it. In such cases it may be more difficult to locate the duct accurately. To aid in its proper identification a very helpful procedure is to insert a hypodermic needle and syringe into the suspected structure to see if it contains yellow bile. Helpful information in difficult cases will also be gained by inserting a needle into the suspected stone before incising the duct. Most of the stones are soft enough to permit the entrance of a needle into them with a characteristic sensation to the surgeon who is familiar with it. Sometimes in cases in which the foramen of Winslow is obliterated the portal vein may be rotated around to a position similar to that normally occupied by the common duct. The use of the hypodermic syringe and the insertion of a needle into the suspected stone will do much to clear up the confusion. Frequently there is a plexus of veins on the duct which bleeds freely when the duct is incised. Some alarm may at first be felt lest the portal vein has been incised. But by applying pressure to the bleeding area for a few minutes it will then be possible in most cases to control the bleeding from the veins on the duct. If the portal vein has been accidentally incised it should be carefully closed by lateral suture and never ligated circumferentially to obstruct its lumen.

We prefer to combine with the operation of *choledochostomy* the removal of the gall bladder. In exceptionally bad risks, however, it is advisable to do the operation in two stages, at the first stage the removal of the stone causing obstruction of the duct, and some time later the removal of the gall bladder. The mortality of operations on cases with stone in the common duct is considerably higher than

<sup>1</sup> Crile, G. W.: The Operative Management of Common Duct Stones, Ann. Surg., 1926, 84, 411.

of those on the gall bladder alone. For that reason every precaution to safeguard life should be undertaken. The removal of the gall bladder is sometimes unusually difficult in these cases because of extensive scarring and adhesions.

The older operations of crushing the stones in the ducts or of breaking them into fragments by passing a needle into them many times are obsolete because there is no assurance that the remaining detritus will be carried away.



FIG. 211.—Operation for removal of a stone in the retroduodenal portion of the common duct. An incision is first made in the parietal peritoneum in order to mobilize the duodenum.

Stones located in the retro-duodenal portion of the common duct are more difficult to locate and to remove. In some cases they can be moved upward into the more accessible supraduodenal portion of the duct; but in other cases this procedure cannot be carried out and it then becomes necessary to mobilize the duodenum in such a way that it can be swung forward to expose the duct. For this purpose Vautrin's<sup>1</sup> operation can be performed as follows: Traction is made on the second or descending portion of the duo-

<sup>1</sup> Vautrin: De l'obstruction calculeuse du cholédoque, *Rev. de chir.*, 1896, **16**, 446.



denum and thus the junction of the intestine and the hepato-duodenal ligament is brought prominently into view. At the point of this junction the peritoneum is incised parallel to the convexity of the duodenal angle and the incision is prolonged along the external border of the second segment of the duodenum to free it from its attachments to the parietal peritoneum. (Fig. 211.) When the duodenum is so freed and turned forward that portion of the duct which is in a groove on the anterior surface of the pancreas becomes exposed. (Fig. 212.) Lower down the duct is often embedded in

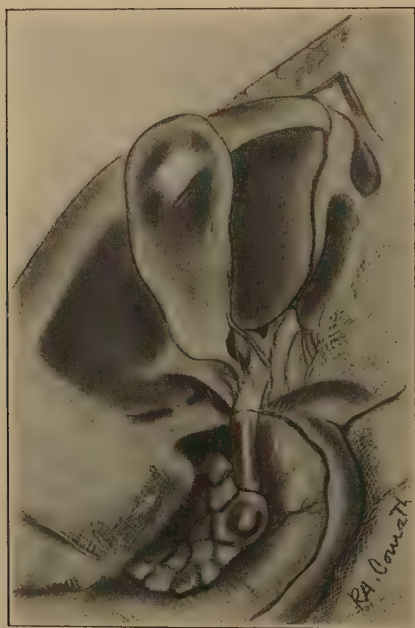


FIG. 212.—The same operation continued. The duodenum has now been mobilized and swung forward, revealing the head of the pancreas and the stone in the common duct.

the pancreas and here the exposure becomes much more difficult. The pancreatic tissue often has to be removed from the posterior aspect of the duct by sharp dissection, and very annoying and troublesome bleeding may occur from many veins. Some of the bleeding may be obviated by using an electro-cautery for this part of the dissection. By Vautrin's procedure the entire common duct can be exposed to a point about  $\frac{1}{2}$  inch (1 cm.) above the ampulla of Vater. (Figs. 213 and 214.) Jurasz<sup>1</sup> reviewed 104 operations

<sup>1</sup> Jurasz, A. T.: Die Mobilisierung des Duodenums, Arch. f. klin. Chir., 1914, 104, 1118.



FIG. 213.—Same operation continued. A longitudinal incision has been made into the common duct and the stone is being extracted.



FIG. 214.—Same operation continued. Suture of opening into the common duct and closure of pancreas over the duct. A drainage tube has been inserted into the duct above location of the stone. A tube, however, can be inserted into the same opening if desired.

from Payr's Clinic in which Vautrin's operation had been carried out with a mortality of 8.5 per cent. In 18 of the cases there was no stone present but instead a dilatation of the duct from chronic pancreatitis and in 1 case from a carcinoma of the pancreas.

Mayo-Robson<sup>1</sup> prefers the transduodenal route for the removal of calculi located in the lower third of the common duct. This operation, sometimes called *duodeno-choledochotomy*, was first performed

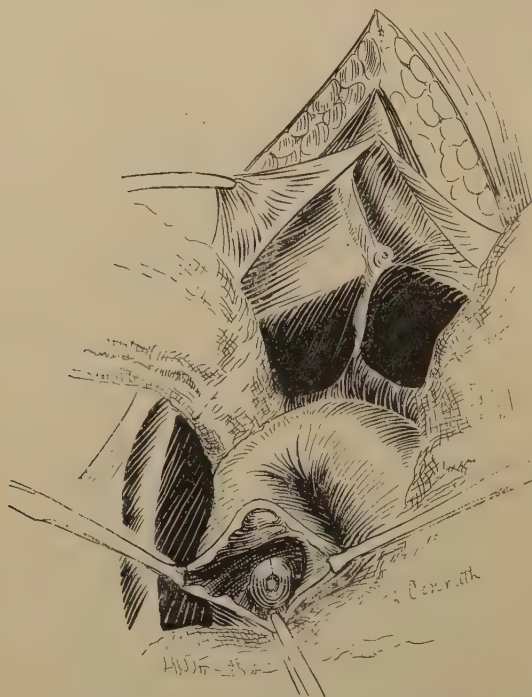


FIG. 215.—Removal through the duodenum of a stone impacted in the biliary papilla. Incision through anterior wall of the duodenum.

by McBurney.<sup>2</sup> It is particularly applicable to stones impacted in the ampulla of Vater. To approach the ampulla of Vater through a duodenal incision Sencert<sup>3</sup> makes the following suggestions: (1) If the ascending colon is fixed (80 per cent of cases), incise the duodenum transversely immediately above that portion or angle of

<sup>1</sup> Mayo-Robson: Diseases of the Gall Bladder and Bile-ducts, 1901, p. 269.

<sup>2</sup> McBurney, C.: Removal of Biliary Calculi from the Common Duct by the Duodenal Route, Ann. Surg., 1898, **28**, 481.

<sup>3</sup> Sencert, L.: Operations sur la portion rétropancréatique du canal cholédoque après mobilization du duodenum, Rev. de gyn. et de chir. abdom., 1906, **10**, 27.

the colon which lies on its anterior surface. (2) If the ascending colon has a mesentery (20 per cent of cases), find the root of the transverse mesocolon and incise the duodenum immediately above this. This leads directly to the ampulla of Vater. When the papilla is found it may be opened by an incision which also splits up the duct, or the stone may be immediately exposed by an incision directly over it through the posterior wall of the duodenum. Usually there is no troublesome bleeding and no sutures need be placed in the posterior wall of the duodenum. The incision in the anterior wall of the duodenum should be closed with a double layer of sutures.

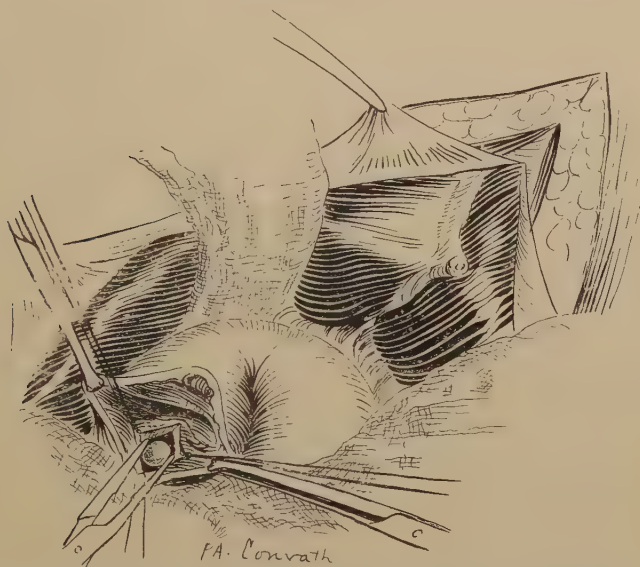


FIG. 216.—Same operation continued. The posterior wall of the duodenum has been incised directly over the stone and the stone is being extracted.

No drainage is required. (Figs. 215 and 216.) Mayo-Robson states that an additional advantage of this operation is that "an incision of the narrow orifice of the bile-duct in the duodenum leaves a patent opening, which will allow any other concretions that may have escaped observation to pass without difficulty." Hancock<sup>1</sup> in 1906 collected 62 cases in which the operation of duodeno-choledochotomy had been performed with an operative mortality of 12.6 per cent. In 57 of the cases the procedure had been carried out for

<sup>1</sup> Hancock, J. C.: The Value and Place of Duodeno-choledochotomy in Gallstone Surgery, *Ann. Surg.*, 1906, **43**, 69.



the removal of gall stones, and in the others for carcinoma of the papilla and for pancreatic calculi. According to Binnie,<sup>1</sup> Kehr and Mayo have supplemented the operation by also opening the common duct high up and pulling strips of gauze through the duct from one opening to the other, thus insuring the removal of all fragments of stone.

**Operative Mortality.**—In our own series there have been 42 cases in which stones have been removed from the common duct. Of this number 5 died, a mortality of 11.9 per cent.

**Recurrence of Symptoms.**—A recurrence of typical symptoms after the removal of a stone from the common duct nearly always signifies either the presence of another stone which was overlooked at the first operation or the formation of a stricture of the duct. There are some who believe that stones can reform within a short time, for example, a few weeks or months; and these surgeons have the opinion that the recurrence of symptoms is often due to a new stone which has been formed. This is a convenient explanation, but there is after all scant evidence to support such an idea. There is no absolute assurance in any case that a stone has not been overlooked. It has been proven at postmortem examinations that a stone may be present even when a fairly large probe or catheter has been passed both upward into each hepatic duct and downward into the duodenum. If, however, a single rounded stone is found in the duct, the presumptive evidence is great that no other stone is present. But the removal of a single facettted stone or of multiple stones from the duct must result in a reasonable doubt as to whether an overlooked one may still remain. There is also always a possibility that an undetected intra-hepatic stone may come down from the liver into the common duct after the operation. In our own series of 42 cases, the symptoms recurred in 1 case; and at a second operation six months later another stone was found which apparently had been overlooked at the former one.

#### TREATMENT OF BENIGN STRICTURE OF THE DUCTS.

When a stricture of the cystic duct is present the condition is most conveniently handled by cholecystectomy, especially since the gall bladder is practically always diseased in such cases.

The most serious types of strictures and those whose treatment is most difficult are the ones which involve the hepatic and common

<sup>1</sup> Binnie, J. F.: *Manual of Operative Surgery*, 1921, 8th ed., p. 582, Philadelphia, P. Blakiston's Son & Co.

ducts. Their origin has already been discussed in Chapter VI. In many of these cases the exposure of the field and the identification of the strictured duct are extremely difficult because of the presence of very dense fibrous adhesions which are often so hard and unyielding as to suggest carcinoma. In fact an operation for the repair of a stricture may be as formidable as any in the surgical repertory. The exposure and the identification of structures are particularly difficult if the gall bladder has been removed at a previous operation. The presence of an external biliary fistula often facilitates the finding of the stricture because the fistula can be followed down right to the duct. It is essential before beginning one of these operations to prepare the patient as well as possible against the dangers of hemorrhage and the effects of severe damage of the liver in accordance with the precautions discussed elsewhere.

Most of the operations which have been devised for the repair of stricture of the common or hepatic ducts are based on one of two general principles, either the use of a tube or a direct anastomosis between the uninvolved portion of duct and the duodenum or stomach. The best prophylactic procedure against the subsequent development of a stricture in a case in which an accidental injury to the duct has occurred during an operation of cholecystectomy is an immediate and direct end-to-end suture of the divided duct over a tube. For a stricture which has already developed many ideas have been suggested, such as:

Dilatation of the stricture and the implantation into the strictured duct of a tube which is led down into the duodenum.

Implantation of a T-tube into the strictured duct with the long arm of the T led out through the abdominal wall.

Resection of the strictured area and end-to-end anastomosis either over a tube or not.

Reconstruction of the excised portion of duct by use of flaps of the duodenum, stomach, omentum, cystic duct, etc.

Direct anastomosis of the hepatic duct to the duodenum or stomach.

Cholecysto-enterostomy or cholecysto-gastrostomy.

Anastomosis of the biliary sinus to the duodenum or stomach.

Anastomosis of the surface of the liver to the duodenum or stomach. This operation, first practised by Kehr, and called *hepato-cholangio-enterostomy*, consists of the removal of a strip of liver tissue about  $2\frac{1}{2}$  inches (6 cm.) long and about 1 inch (2 cm.) wide. With an actual cautery a sufficiently deep opening is made into the liver to expose several bile-ducts of moderate size. A loop

of small intestine, preferably duodenum, is sutured directly to the edges of the incision in the liver. The operation has become practically obsolete because of unsatisfactory results. There is but little or no anastomosis between the bile-ducts of different lobes of the liver, or, for that matter, between those of the same lobe. For that reason drainage from a few ducts is not likely to have a very beneficial result in a case of obstruction of the major bile trunks from the liver.

McArthur<sup>1</sup> was probably the first to utilize the principle of the rubber tube in the reconstruction of the common duct. He advocated the use of a tube the end of which has been turned back on

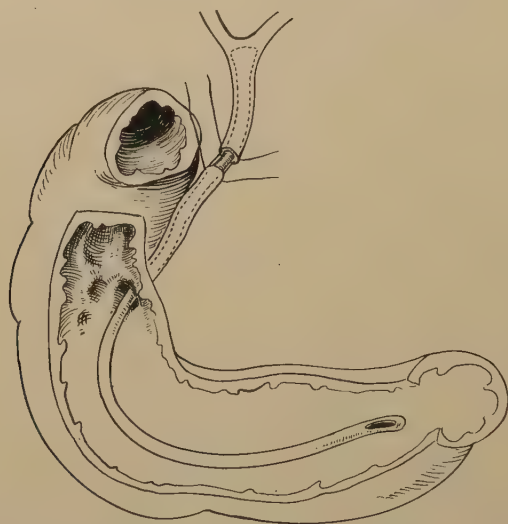


FIG. 217.—Diagram showing McArthur's method of utilizing a rubber catheter for the reconstruction of the common bile duct.

itself twice to make a double revere. This end of the tube is placed in the duct, and the revere allows it to be held in place better than a plain tube. The other end is inserted into the duodenum, and at least 3 or 4 inches are allowed to lie in the lumen of the intestine. (Fig. 217.) The purpose of the latter recommendation is to permit the peristaltic waves to grip the end and thus ultimately to insure the passage of the tube. Later McArthur recommended the use of an ordinary catheter with the wide end placed in the duct. Sullivan<sup>2</sup> did much to popularize the use of a rubber tube in opera-

<sup>1</sup> McArthur, L. L.: Repair of the Common Bile-duct, *Ann. Surg.*, 1923, **58**, 129.

<sup>2</sup> Sullivan, A. G.: Reconstruction of the Bile-ducts, *Jour. Am. Med. Assn.*, 1912, **58**, 2086.

tions for the reconstruction of the bile-ducts, after showing the possibilities in experiments on dogs. He proposed the insertion of a rubber tube, with a lumen of not less than  $\frac{1}{4}$  inch in diameter, into the hepatic duct and fixing it there with 2 or 3 non-absorbable sutures. The other end was pushed down through the stump of the common duct into the duodenum for about 1 inch. When the stump could not be found, Sullivan recommended puncturing the duodenum, inserting the tube through the puncture, and folding the wall of the duodenum around it in a manner similar to that employed in Witzel's gastrostomy. Any exposed, free portion of tube was united to the edge of the gastro-hepatic ligament and covered with the great omentum which was held in place with sutures. One of the difficulties with this type of operation is the recurrence of stricture after the tube has been passed. To minimize this danger it is very important to bring the ends of the duct together whenever possible so that no considerable length of scar tissue will be formed.

The use of a tube in some manner is the most generally applicable principle in the repair of strictures of the duct. One unsatisfactory feature, however, is that the stricture is very likely to contract again as soon as the tube has been passed. This risk is of course greater if the stricture is a long one. To prevent as much as possible this occurrence the idea naturally suggests itself of encouraging the tube to stay in the duct as long as it will. This can best be done by using a tube which is too short to project into the duodenum but whose lower end is about at the level of the beginning of the common duct sphincter in the wall of the duodenum. A tube in such a position cannot be grasped by peristaltic contractions of the duodenum and carried downward. It will, however, very probably eventually become encrusted with bile salts, and it is of course a foreign body. We placed a tube in such a position in a tightly strictured common duct in which the stricture extended to the liver. It seemed impossible to perform an hepatico-duodenostomy; and it was necessary to dilate this stricture forcibly before inserting the tube. The lower end of the latter was then left just above the common duct sphincter. It has now been present for nine months. The patient has gained 30 pounds and considers herself in perfect health. The purpose in desiring the tube to remain in this case is to keep the stricture from contracting down.

The principle of resection of the strictured area and end-to-end anastomosis of the ends of the duct is impossible to carry out in the majority of cases because of technical difficulties. The reconstruction of an excised portion of duct by means of various flaps from the duo-



denum, stomach, etc., is not so difficult technically but the results are often unsatisfactory because the flap later becomes substituted by scar tissue. Direct anastomosis of the hepatic duct to the duodenum or stomach by uniting the proximal stump of the duct directly to one of these organs is not entirely free from the danger of a later development of a stricture at the site of the anastomosis. A greater danger, however, is the same as that which occurs with cholecysto-enterostomy or cholecysto-gastrostomy, namely, a serious infection

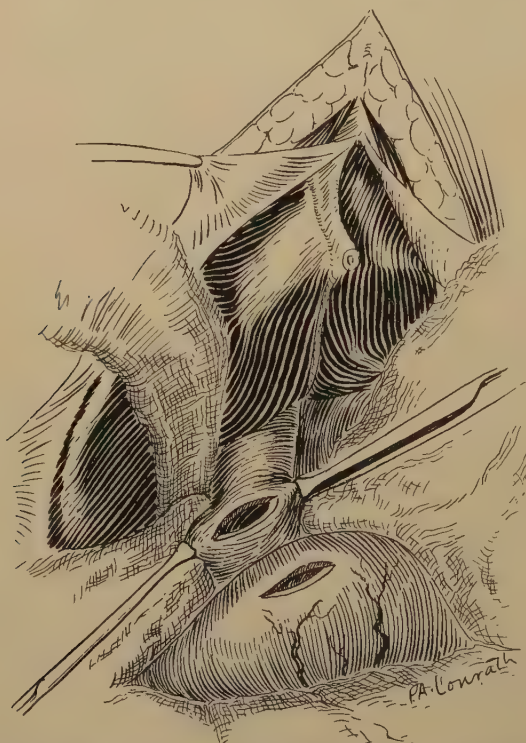


FIG. 218.—Direct anastomosis of a dilated common duct to the stomach or duodenum.

of the liver from the passage into the bile-duct of duodenal or gastric contents. (Figs. 218, 219 and 220.)

The operation of cholecysto-enterostomy or cholecysto-gastrostomy is performed in a manner identical with the operation of gastro-enterostomy except that the gall bladder is united to the duodenum or the stomach as the case may be. The natural physiological conditions are of course more nearly approximated if the gall bladder is anastomosed to the duodenum than if it is joined to the stomach.

From the standpoint of the effects of the operation on the human it seems to make little or no difference whether the bile pours into the duodenum or stomach. But in the recent experimental study made by J. S. Horsley, Jr.,<sup>1</sup> there was a much higher mortality after cholecysto-duodenostomy. This operation is seldom possible in cases of benign stricture of the duct because in most of such cases the gall bladder has already been removed. Excellent experimental studies of these operations have also been made by Gatewood and



FIG. 219.—Same operation continued. The technique is essentially the same as that of an ordinary gastro-enterostomy.

Pappins<sup>2</sup> and by Lehman<sup>3</sup> as well as by Horsley; and a clinical review of the subject of cholecysto-gastrostomy has been presented by Jacobson.<sup>4</sup> The operation should be regarded as one which gives only

<sup>1</sup> Horsley, J. S., Jr.: Experimental Study of Cholecysto-gastrostomy and Cholecysto-duodenostomy, *Southern Med. Jour.*, 1927, **20**, 669.

<sup>2</sup> Gatewood and Pappins, P. H.: Cholecysto-enterostomy from an Experimental Standpoint, *Surg., Gynec. and Obst.*, 1922, **35**, 445.

<sup>3</sup> Lehman, E. P.: Hepatitis following Cholecysto-gastrostomy, *Arch. Surg.*, 1924, **9**, 16.

<sup>4</sup> Jacobson, J. H.: Anastomosis of the Gall Bladder to the Stomach: Cholecysto-gastrostomy, *Am. Jour. Obst.*, 1914, **70**, 825.

temporary benefit because serious infection of the liver is an almost inevitable consequence. The principal reason for the infection of the liver is the regurgitation of duodenal or gastric contents into the gall bladder. Coffey<sup>1</sup> in 1909, in discussing the transplantation of the common bile-duct in operations for the removal of the pancreas, called attention to the importance of the normal oblique passage of the duct through the wall of the duodenum as a factor of safety in preventing the regurgitation of duodenal contents into the duct.



FIG. 220.—The same operation completed.

The normal arrangement of the duct provides it with a valve-like mechanism which is a safeguard against a reflux from the duodenum. In all operations which are based on the principle of a direct anastomosis of the biliary with the alimentary tract the important normal anatomical arrangement cannot be duplicated; and therefore regurgitation of contents occurs. (Figs. 221, 222, 223 and 224.)

A direct anastomosis of the biliary sinus to the duodenum or

<sup>1</sup> Coffey, R. C.: Pancreato-enterostomy and Pancreatectomy, *Ann. Surg.*, 1909, 50, 1238.

stomach has been made successfully in a few instances in which it was found to be impossible to recognize the proximal stump of the



FIG. 221.—The operation of anastomosing the gall bladder to the stomach or duodenum. The first sutures have been placed and the gall bladder and stomach have been opened.

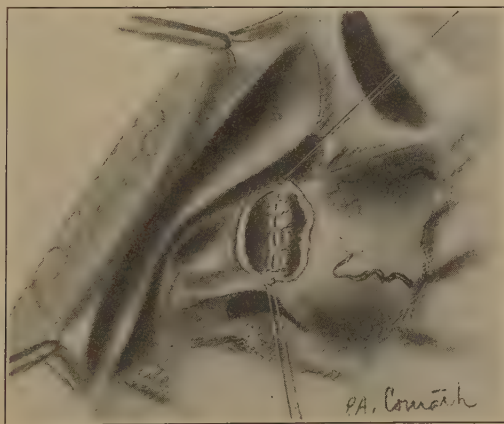


FIG. 222.—The same operation continued.



common or hepatic duct. This operation, however, can hardly be looked upon as the most desirable type, since almost certainly in many cases the scar tissue will contract again with recurrence of the

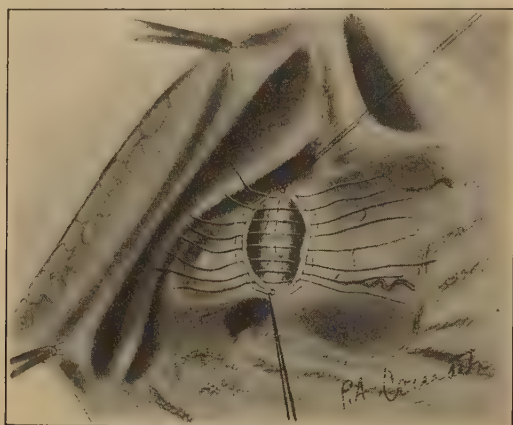


FIG. 223.—The same operation continued.



FIG. 224.—The same operation completed.

symptoms. Several excellent results, however, have been reported after the use of this method. Douglas<sup>1</sup> states that Lahey in 1924 reported 3 cases, 1 of which had remained well for two years after

<sup>1</sup> Douglas, J.: Strictures and Operative Injuries of the Bile-ducts, *Ann. Surg.*, 1926, **84**, 392.

anastomosis of the sinus to the duodenum. In another case of anastomosis of the sinus to the stomach the patient had been well for eleven months except for two attacks of jaundice and chills. Lilienthal implanted a fistula into the pyloric portion of the stomach, and the patient was well four years later. St. John also reported a case of a similar operation in which the patient had been free from symptoms for twenty-one months afterward.

### LATE RESULTS OF OPERATIONS FOR RECONSTRUCTION OF THE COMMON DUCT.

As in cancer cases the surgeon should not be too optimistic about the late results of these operations merely because the patient survives the operation and does well for a few months. There have been three excellent comprehensive studies of the late results. The first was by Eliot<sup>1</sup> in 1918; the second was by Eisendrath<sup>2</sup> in 1920; and the most recent one was by Douglas<sup>3</sup> in 1926, referred to above. Since the article by Douglas includes not only the material in the two previous reports but also 12 cases from St. Luke's Hospital of New York, we shall quote extensively from his article.

"Analysis of these 12 cases from St. Luke's Hospital shows that 5 are well and free from symptoms from one and a half to six years after operation. Of these, 2 had second operations. All were cases of suture of the ducts. Three were over a T-tube. One with no tube drainage was well six years later. One with the tube led out through the common duct below the point of repair was well six years. Two had reappearance of symptoms after operation which lasted four to twelve months, but are now symptom-free eighteen months to four and a half years after operation. One patient had an hepatico-duodenostomy and was well nine months; recurrence due to narrowing of the lumen and obstruction from inspissated bile; reoperation and return of symptoms two months later. One patient was well almost two years after immediate end-to-end suture, then reoperated upon, stricture cut and T-tube inserted. Sinus never closed, symptoms occurred at intervals, and patient died one and a half years later of mesenteric thrombosis. One died after four operations during eight years. One after a third operation in another hospital.

<sup>1</sup> Eliot, E., Jr.: The Repair and Reconstruction of the Hepatic and Common Bile-ducts, *Surg., Gynec. and Obst.*, 1918, **26**, 81.

<sup>2</sup> Eisendrath, D. N.: Operative Injury of the Common and Hepatic Bile-ducts, *Surg., Gynec. and Obst.*, 1920, **31**, 1.

<sup>3</sup> Douglas, J.: Strictures and Operative Injuries of the Bile-ducts, *Ann. Surg.*, 1926, **84**, 392.

Two died of secondary hemorrhage after drainage operations. Another died after a repair in another hospital.

"It is obvious that no justifiable conclusions could be based on this series alone. Study of other series is of interest. Judd reports 10 cases. Of these, 4 died (2 as an immediate result of operation), 1 two years and 1 four months after hepatico-duodenostomy. Three cases were well and symptom-free. One in which stricture was divided and T-tube used was well seven and a half years. One repair of defect by insertion of a piece of cystic duct was well seven and a half years. One of transverse suture after splitting of stricture and use of T-tube was well three and a half years after two years of symptoms. Three cases still complained of some symptoms. One case had three operations—division of stricture and T-tube, a lateral anastomosis and an hepatico-duodenostomy; patient was in good health for three years, but at times jaundiced. One case had two operations, in both of which the stricture was cut and a T-tube inserted; patient was in good health for two years but has had recurrence of pain. Another case had two operations, both hepatico-duodenostomies one year apart; and one and a half years later the patient had attacks of pain and jaundice.

"Seven cases of hepatico-duodenostomy are reported by Erdmann. Two died. One case was well five years after second operation (hepatico-duodenostomy). Another case was well five years after operation. One case had two operations and was not reported cured. One case, tube in place eleven months, reported well three months later. Another case, reoperation five months after hepaticoduodenostomy and reported as only convalescent.

"McArthur has reported 5 cases of repair of the ducts over a tube into the duodenum. The point of importance in these cases was the use of a cuffed tube or the funnel end of the tube which was placed in the duct above the stricture, a long portion of the tube going into the duodenum.

"A personal communication recently received from Dr. McArthur gives the final report in these cases. Case I died two years after operation from carcinoma of the stomach. Case II died one and a half years after operation from septic cholangitis from the presence of a short tube that never passed, as described in his paper. Case III is still alive and free from jaundice eight years after operation, but every month or so has an attack of chills, fever and vomiting, suggesting intermittent cholangitis. Patient had a gastro-enterosotomy five years ago for pyloric stenosis. Case IV still well. Case V operated on in 1913 by Dr. Finney who found stone in the

common duct which contained a fragment of rubber, probably from a small portion of the catheter. Believes patient is still alive."

Of the series of 51 cases from the literature reported in the articles by Eisendrath, the result after one year is given in only 4 cases. The rest, in which any time is mentioned, are reported as well four to ten months after operation. The others are reported as dead as a result of operation, or recovered. One is reported as again having symptoms. Douglas states, "There are 5 cases of operative injury with immediate transverse suture of the hepatic duct over a T-tube, quoted from Kehr, with the report, 'all recovered and remained permanently well,' but with no detail as to time mentioned."

From the published reports of cases it is difficult, if not impossible, to state which method of repair gives the best results. Because of different conditions encountered in different patients any one type of operation is not applicable to all cases. In general, however, it would seem that the best results follow an immediate repair of the duct either with or without a tube. Judd<sup>1</sup> in a recent article concludes that the most satisfactory operation is the anastomosis of the common duct or the opening in the surface of the liver to an opening in the duodenum over a tube. Eliot states that 1 of W. J. Mayo's patients in whom the hepatic duct was implanted into the duodenum was well fifteen years later, 1 reported by Summers was well seven years later, 1 by Bazy four years, 1 by Mann four years, 1 by Crile three years and 1 by Wilms fifteen months. He also states that Dujarier reported a case well three years and O'Day a case well six years after implantation of the hepatic duct into the stomach.

Douglas has suggested the administration of bile salts by mouth in order to stimulate the flow of bile after operations for strictures of the duct and thus to aid in keeping the canal open. But the contraction of a stricture is a very slow process involving months and even years. To be effective, therefore, it would be necessary to continue the bile salts almost indefinitely.

### **CARCINOMA OF THE PROXIMAL PORTION OF THE COMMON BILE-DUCT.**

A small number of the comparatively few new growths of the common bile-duct are amenable to radical excision. During the operable stage a carcinoma of the common duct is a hard, gray,

<sup>1</sup> Judd, E. S.: Stricture of the Common Bile-duct, *Ann. Surg.*, 1926, **84**, 404.



well-defined growth, which may be mistaken for a stone. Great care must be used during excision of a portion of the duct not to injure important neighboring structures. An end-to-end anastomosis of the divided ends of the duct remaining after resection of the tumor may be possible in a few instances. Fine catgut sutures are passed in the posterior aspect of the walls of the ends of the duct and are tightened slowly. Approximation by sutures of the tissue surrounding the ends of the duct will aid in their apposition. A rubber T-tube or a Halsted hammer is now inserted into the duct. Moynihan prefers to pass a rubber tube upward toward the liver and another one toward the duodenum. More sutures are then placed through the anterior wall until it is closed about the tubes.

If it is impossible to approximate the divided ends of the common duct, after a resection of a portion of it, the distal end may be ligated and the proximal end implanted into the duodenum or stomach by the operation of hepato-duodenostomy or hepato-gastrostomy. The common hepatic duct may be treated in the same manner. An alternative procedure is to ligate both of the divided ends of the duct and perform a cholecysto-enterostomy.

Palliative operative measures must be used when radical excision of the new growth of the common duct is impossible. Several methods are available for handling the situation. The simplest of these is drainage of the common duct (choledochostomy) proximal to the occlusion. The dilated proximal portion of the duct has been anastomosed to the duodenum and other portions of the intestinal tract (choledoch-enterostomy). Usually, however, it is simpler to secure internal drainage of the obstructed biliary tract by anastomosing the gall bladder to some portion of the intestinal tract. An anastomosis of the gall bladder to the duodenum (cholecysto-duodenostomy) or to the stomach (cholecysto-gastrostomy) is preferable to its anastomosis to the colon (cholecysto-colostomy). The operation of cholecysto-enterostomy has been discussed elsewhere.

#### **CARCINOMA OF THE TERMINAL PORTION OF THE COMMON DUCT INCLUDING THE PERIAMPULLARY REGION OF THE DUODENUM.**

According to Rolleston one-third of all new growths of the bile-ducts arise in the terminal portion of the choledochus. The tumor tends to grow along the course of the duct. Local metastases are frequent, involving the lymph nodes on the posterior surface of the

head of the pancreas and those in the pancreatic and duodenal angles. Metastases to the liver are frequent. Gall stones are usually not associated with malignancy of the duct.

A recent paper by Cohen and Colp<sup>1</sup> considers cancer of the periampullary region of the duodenum. These authors find that ampullary carcinomata normally remain local and are late to metastasize. Though this type of malignancy during its operable stage is small, varying in size from a pea to a walnut, it causes obstruction to the ducts of the liver and pancreas. Grossly these tumors may be pedunculated growths or the ulcerating plaque type of tumor.

Although the anatomical situation of new growths of the periampullary region makes radical extirpation difficult, several case reports have been made of successful operations. Radical excision was performed at the Mount Sinai Hospital in 3 out of 8 cases of periampullary carcinoma of the duodenum reported by Cohen and Colp. These authors have reviewed the literature on the subject and have collected 59 cases of radical operation for carcinoma of the periampullary region. In 53 of these 59 cases, the tumor was excised by opening the duodenum. The mortality in this group of cases was 44 per cent.

Several technical features are stressed by Cohen and Colp. The duodenum is opened by a vertical anterior incision after the duodenum has been properly mobilized. Small pedunculated tumors may be removed with a scalpel, endotherm knife or cautery. It may be necessary to remove a portion of the duodenal wall and a portion of the common bile and pancreatic ducts. The defect in the duodenum should be carefully closed and the ducts reinserted into the duodenum, according to the principles advocated by Coffey discussed on page 444. The operation of papillectomy may be combined with the temporary drainage of the gall bladder or common duct. Since the danger of the formation of a duodenal fistula is considerable after such an operation the duodenal wall should be carefully closed by three layers of suture. Complete hemostasis should be made throughout the operation.

In some cases papillectomy will not suffice to get beyond the carcinoma. It is necessary to make a circular resection of the duodenum and partial pancreatectomy. This operation is one of the first magnitude and should seldom be attempted on such poor operative risks as these patients. A successful operation of this type was

<sup>1</sup> Cohen, I. and Colp, R.: Cancer of the Periampullary Region of the Duodenum, Surg., Gynec. and Obst., 1927, **45**, 332.

performed by Halsted.<sup>1</sup> He reported the successful removal of a primary carcinoma of the duodenal papilla by operation. He excised a large circular portion of the duodenum,  $\frac{3}{4}$  inch of the common duct and a piece of the pancreatic duct. An end-to-end anastomosis of the duodenum was made and the bile and pancreatic ducts were transplanted into the duodenum. Later a cholecysto-duodenostomy was performed. The patient lived several months, dying of recurrence.

Springer<sup>2</sup> has advocated the two-stage operation suggested by Kausch. A preliminary cholecysto-enterostomy is made for the relief of jaundice. The second stage of the operation consists of radical excision of the tumor and possibly a gastro-enterostomy. Upcott<sup>3</sup> and Abell were the first to apply radium to involved glands in the gastro-hepatic omentum left behind after papillectomy. Five mg. of radium were inserted by means of a probe into the opening of a cholecystotomy into the cystic duct eleven days after operation. Abell applied radium directly to a papillary growth after duodenotomy. Two tubes containing 25 mg. of radium were anchored to the growth by catgut sutures. The tubes were removed twelve hours later by means of a heavy silk string which had been passed through the esophagus and stomach and tied to the tubes containing the radium.

If upon abdominal exploration the carcinoma in the periampullary region cannot be excised, due to its size and location, some type of drainage operation to relieve the obstructed ducts is indicated.

#### LATE RESULTS OF RADICAL OPERATIVE REMOVAL OF CARCINOMA OF THE AMPULLARY REGION.

In the 59 cases collected by Cohen and Colp 1 case operated on by Kelly was alive nine years later; 1 case of Oliani's was alive four years later; 1 of Körte's three and three-quarters years later; 1 of Tenani's and 1 of Pozzi's each alive three years later; 1 of Hartman's eighteen months later; 1 of Propping's and 1 of Müller's each alive and well after one year. Several other cases were reported as alive and well after a few months; but some others died of recurrences from one year to a year and a half after the operation.

<sup>1</sup> Halsted, W. S.: Contributions to the Surgery of the Bile Passages, Especially of the Common Bile-duct, *Boston Med. and Surg. Jour.*, 1899, **141**, 645.

<sup>2</sup> Springer, Ernest: New Growths Involving the Terminal Bile and Pancreatic Ducts, *Boston Med. and Surg. Jour.*, 1925, **192**, 997.

<sup>3</sup> Upcott and Abell: Quoted from Cohen and Colp.

**SURGICAL TREATMENT OF BILIARY FISTULÆ.**

External biliary fistulæ usually lead either from the gall bladder or from one of the ducts. Those which lead from the gall bladder are best treated by cholecystectomy. If the discharge after a cholecystostomy is of mucus without bile, there is a clear indication of an obstruction of the cystic duct which most commonly is due to a stone impacted in the duct. This condition like the previous one is best treated by the removal of the gall bladder and duct in such a way as to include the stone in the removed tissue. Because of extensive adhesions the dissection in this type of case is sometimes very difficult, and great care must be exercised not to injure important structures.

The type of external biliary fistulæ which lead from the hepatic or common ducts are usually due to stricture of the duct below the point of escape of the bile. Such fistulæ should be treated in accordance with the plans of treatment of stricture which have been discussed elsewhere in this chapter.

Internal biliary fistulæ which lead into the alimentary canal should be treated largely according to the associated pathology; and great care should of course always be exercised to close the opening into the intestine or the stomach as the case may be. One of the great dangers in these cases is that the opening into the intestine will not be recognized at the time of operation. If a gall bladder is so firmly adherent to the intestine that sharp dissection is required to separate it suspicion should be aroused as to the possibility of a communication between the two viscera, and accordingly a careful search should be made for a possible opening into the intestine. In the cases in which the gall bladder communicates with the intestine cholecystectomy should be done as a rule. If the fistula is from the common or hepatic ducts calculi will generally be found in the duct and these should be removed. If the lumen of the duct is patent throughout its course it is better to insert a tube and drain the duct rather than to attempt to close the opening. As a rule the gall bladder is also badly diseased in these cases and should be removed. Occasionally an abscess from around one of the ducts perforates through the diaphragm and into the lung so that bile is expectorated. In such cases it is important to aspirate the bile from the pleural cavity; and if an empyema develops, to establish drainage as in any other case of empyema. It may also be necessary to treat by radical measures an area of suppuration in the lung if such occurs, although usually conservative measures should be tried first.



## HEPATIC INSUFFICIENCY.

Surgical operations upon greatly debilitated patients suffering from obstructive jaundice are attended with great risk from the complications of hemorrhage, uremia and a clinical syndrome which has been called by some hepatic insufficiency. Walters and Parham<sup>1</sup> have described this clinical picture as follows:

**"Clinical Picture of Hepatic Insufficiency.**—Usually the first two to eight days after operation the course is uneventful; biliary drainage and urinary output are normal, fluids are taken well, the pulse and temperature are normal. One of the first signs of the onset of trouble is paling and thinning of the bile with marked increase in the flow. This profuse cholerrhagia does not continue long, but the bile remains thin. The patient grows weaker, the pulse loses volume, and the temperature becomes subnormal. Restlessness and irritability develop with great fatigue and muscular weakness. Soon regurgitant vomiting follows intake of liquids by mouth and little taken by rectum is retained. Jaundice does not deepen markedly, but there is an increasing pallor beneath the icteric hue, the face becomes drawn, and the eyes anxious. The patient grows progressively weaker and finally dies. The urinary output remains proportional to the fluid intake throughout, and the urine reveals little or no evidence of marked nephritis. The blood-urea remains persistently low."

The symptoms due to the failure of the liver may be intimately associated with nephritis. Instead of an increase in the flow of bile from a drainage tube there may be a sudden diminution in the amount with resultant deepening of the jaundice. Albumin and casts may appear in the urine and the blood-urea becomes elevated. The concomitant renal failure may result in death in uremic coma.

Whipple<sup>2</sup> has described a symptom-complex, practically the same as that given by Walters and Parham for hepatic insufficiency, as being due to pancreatic asthenia. Some of his patients with pancreatic lesions had an associated biliary disease. Though it is possible that there may be involvement of the pancreas in the various stages of biliary disease, we have felt that the condition which has been described as hepatic insufficiency arose primarily from derangement of the liver rather than the pancreas.

<sup>1</sup> Walters, Waltman and Parham, Duncan: Renal and Hepatic Insufficiency in Obstructive Jaundice, *Surg., Gynec. and Obst.*, 1922, **35**, 605.

<sup>2</sup> Whipple, A. O.: Pancreatic Asthenia as a Postoperative Complication in Patients with Lesions of the Pancreas, *Ann. Surg.*, 1923, **78**, 176.

Besides the features of the syndrome which have been mentioned we have been impressed by the rapid loss of weight, low blood-pressure, the small liver and the occasional low blood-sugar.

Differentiation of the coincidental factors of hepatic and renal failure in the deeply jaundiced patients may be difficult. Wilensky and Colp<sup>1</sup> have made an extended study of the nitrogen bodies in such cases and have concluded that nitrogen retention occurs in but a small proportion of all cases in which renal damage occurs. They believe the sequence of events in lesions of the biliary tract are a primary effect on the hepatic cells and a secondary effect on the renal epithelium.

### NON-SURGICAL TREATMENT OF DISEASES OF THE BILIARY TRACT.

The surgical treatment of diseases of the biliary tract has become so well established as the one of choice that only scant mention need be made of non-surgical measures. When the causes of cholecystitis and particularly of the formation of gall stones become better understood it is reasonable to suppose that much more can be done to prevent these conditions than is now possible at the present time. The non-surgical measures should be planned with reference to combatting existing infection, control of any existing gastro-enteritis, avoiding as much as possible those foods which are thought to induce the formation of gall stones because of their high content of cholesterol, the securing of better drainage of bile, the improvement of any associated cardiac or renal disease, the improvement of a badly damaged liver, the control of pain, etc.

It is doubtful if any particular drug has an important effect in the treatment of cholecystitis. Hurst and Knott,<sup>2</sup> however, are convinced that urotropin in large doses (as much as 100 gr. taken three times a day) is of definite value. Their conclusions are based largely on the finding that the bile becomes sterile after such treatment, but for reasons presented in Chapter III, this fact is no criterion of whether or not the cholecystitis is improved. Lyon's method of non-surgical drainage (see page 175) may be of some help; but again in this connection it must be recalled that cholecystitis is a disease of the wall of the gall bladder and it is doubtful how

<sup>1</sup> Wilensky, A. O. and Colp, Ralph: Relation of Nitrogen Bodies of the Blood to Surgical Problems in Liver and Biliary Tract Disease. III. Status of Nitrogen Bodies of Blood in Severe Cases of Biliary Tract Disease and its Use in Differentiating a Terminal Hepatic and a Terminal Renal Group of Cases, *Arch. Surg.*, 1927, **15**, 635.

<sup>2</sup> Hurst, A. F. and Knott, F. A.: Discussion, *British Med. Jour.*, 1926, **ii**, 677, 678.

effective a simple drainage of bile may be. The same may be said of the various waters, such as Carlsbad, etc. The fact that many patients feel better under the rest and vacation enjoyed at various spas and watering places is no indication as to whether or not their biliary disease has really been cured, particularly since cholelithiasis notoriously has intermissions of improvement.

Dieting also is of doubtful value so far as any permanent effect on a case of cholecystitis is concerned. McNee<sup>1</sup> has said very aptly that he could see no way of cutting off the small amount of cholesterol that the body needed to replace wastage from the cholesterol metabolism, if one were to give an adequate although modified diet. "The metabolism of cholesterol in the body is as conservative as iron metabolism, and it would be almost as logical to try to cure erythremia by removing the iron in the food required for hemoglobin."

#### **RADIOTHERAPY FOR TUMORS OF THE BILIARY TRACT.**

The treatment of tumors of the biliary tract by the  $x$ -ray and by radium has up to the present been very unsatisfactory. Mention has already been made on page 452 of the work of Upcott and of Abell with radium. Our own experience with radiotherapy for tumors of this region has been decidedly disappointing; and we know of no satisfactory results obtained by others.

<sup>1</sup> McNee, J. W.: Discussion, British Med. Jour., 1926, ii, 680.

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"Ye labor and ye patience, ye judgment and ye penetration  
which are required to make a good index is only known to those  
who have gone through with this most necessary and painful but  
least-praised part of a publication."

WILLIAM OLDYS, 1687.\*

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